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ORIGINAL ARTICLE

Post-operative Outcomes of Pituitary Macroadenoma Patients in a Tertiary Hospital in the Philippines

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Abstract

Background. Pituitary adenomas comprise approximately 20% of surgically resected intracranial tumors. This study aimed to collect local data on the post-operative neurologic, visual and endocrine outcomes of patients with pituitary macroadenoma.

Methodology. This is a retrospective study of patients with pituitary macroadenoma who underwent neurosurgery at the Philippine General Hospital between 2017 to 2022. Data on demographics, clinical signs and symptoms, neuro-ophthalmologic examination findings, hormonal and radiologic studies, type of surgery, and post-operative outcomes were collected. Statistical analyses were done to compare the neurologic, ophthalmologic and endocrine status pre- and post-operatively.

Results. A total of 122 patients were included. The mean age was 44.18 years, and majority (50.82%) were female. The most common presentation was blurring of vision. Most tumors were non-functioning (77.87%). Among the functioning adenomas, the most common was acromegaly. The median tumor size was 3.5 cm, and the median time to surgery was 18 months. Microscopic transsphenoidal surgery was the most common approach (60.83%) followed by endoscopic resection (24.17%). There was significant improvement in visual acuity post-operatively (p >0.05), by approximately one line in the Snellen chart. There was also some improvement in post-operative endocrine function, manifested as a significant decrease in the use of hormone replacement therapy. Factors such as age, sex, type of adenoma, tumor size, timing of surgery, surgical approach, post-operative complications and adjuvant radiation were not significantly associated with the visual and endocrine outcomes (p >0.005).

Conclusion. This is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients. Our results showed that even patients with longstanding visual and endocrine deficits may still improve with surgery.

Key words: pituitary macroadenoma, pituitary surgery, post-operative outcomes, Philippines

INTRODUCTION

Pituitary adenomas comprise approximately 20% of all surgically resected intracranial tumors.[1-3] While epidemiologic data vary due to different factors, the estimated annual incidence is 3 to 94 cases per 100,000, with an overall estimated prevalence of 16.7%.[1,3,4] Despite its benign characteristics, this tumor exerts significant medical and socioeconomic burden on patients, especially since it commonly affects those in the working age group (second to fourth decade of life).[5] The most common clinical presentations are visual impairment and endocrinopathy, due to the proximity of the tumor to the optic chiasm and effects on other functions of the pituitary gland.[3] This holds true particularly for pituitary macroadenomas, which are tumors that are at least 1 cm in greatest diameter.[1,3] Without prompt and adequate treatment, pituitary adenomas can increase in size, causing further compression of the optic apparatus and leading to complete blindness in some cases.[4,6,7]

In high-income countries, early detection and treatment are feasible due to access to health coverage, social security and advanced neurosurgical care, making it

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easier for patients to seek consult even if they only have mild signs and symptoms.[8] On the other hand, in low- and middle-income countries (LMIC) like the Philippines, socioeconomic factors come into play, affecting health-seeking behavior and contributing to delay in treatment.[8] In addition, pituitary surgery is usually performed in larger tertiary centers, limiting the number of operations performed in the country.

There is paucity of local data regarding the post-operative outcomes of patients with pituitary macroadenoma. In this study, we determined the neurologic, visual, and endocrine outcomes of patients who underwent surgery for pituitary macroadenoma, quantified the amount of delay between symptom appearance and treatment, and correlated it with the visual and endocrine outcomes. To the authors' knowledge, this is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients.

METHODOLOGY

This is a retrospective study describing the demographic and clinical characteristics and outcomes of pituitary macroadenoma patients who underwent neurosurgery at the Philippine General Hospital between 2017 to 2022. Total enumeration of all eligible samples was done. All pituitary macroadenoma patients of pediatric to adult age seen by the neurosurgery service in the period specified were included in the study. Histopathology results were reviewed to ascertain the diagnosis of pituitary macroadenoma. Patients diagnosed with pituitary microadenoma, presented with a recurrent tumor, underwent surgery at another institution, underwent medical management only, or had missing medical records were excluded. Patients with final histopathology results other than pituitary macroadenoma (sellar-suprasellar meningioma, craniopharyngioma, glioma and adenocarcinoma) were likewise excluded in the study. This study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB 2023-0650-01). Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patient information was obtained from the databases of the multidisciplinary team managing pituitary tumor patients (neurosurgery, endocrinology, and ophthalmology), after which chart review was performed. Data on age, sex, clinical signs and symptoms, neuro-ophthalmologic examination findings [visual acuity, visual field perimetry, optical coherence tomography (OCT)], hormonal and radiographic studies, type of surgery, extent of resection, post-operative complications, and post-operative outcomes were collected. The timing of surgery in relation to symptom onset was recorded, in order to quantify delays. Post-operative clinical status, ophthalmologic examination findings and hormonal levels were assessed at two time points: at the immediate post-operative period (within 48 hours) and on the latest follow-up date.

a. Pre- and post-operative visual conditions were determined using the best corrected visual acuity classification used by the World Health Organization. These were categorized as mild (visual acuity 20/40 to 20/60),
b. moderate (worse than 20/60 to 20/200),
c. severe (worse than 20/200 to 20/400), and
d. blind (worse than 20/400).[9]

The best corrected visual acuity was recorded in both Snellen and logMAR notation. Pre- and post-operative visual field defects were also compared.

Endocrine assessments were based on comparison of baseline pre- and post-operative pituitary panels and use of medications. Since majority of pre-operative hormonal tests were done in laboratories outside the hospital, results were based on the available normal reference range. Different hormonal panels were evaluated for the pituitary hormonal axes: serum cortisol and plasma adrenocorticotropic hormone (ACTH) for corticotrophs; luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and testosterone for gonadotrophs; serum thyroid-stimulating hormone (TSH), free T4 and T3 for thyrotrophs; serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1) for somatotrophs; serum prolactin (PRL) levels for lactotrophs; and posterior pituitary function based on the presence of diabetes insipidus (DI). Dynamic testing of hypothalamic-pituitary axes such as 1 mg dexamethasone suppression test or growth hormone test with 75 g oral glucose were done by the endocrinology team in cases where there was a consideration of hyperfunctioning pituitary tumors. Assessment and characterization of hormonal dysfunction were based on pre-operative hormonal levels and diagnosis of the endocrinology team. In addition, patients were classified with pre-operative hypopituitarism if there is partial loss of anterior and posterior pituitary gland function leading to at least one abnormal endocrine axis prior to surgery, and with panhypopituitarism if three or more endocrine axes were deranged.

The diagnostic criteria for DI consisted of polyuria (≥250 mL for two consecutive hours), hypernatremia (serum Na level >145 mEq/L) and urine specific gravity (USG) of ≤1.005.[10] A patient was diagnosed with DI if there were clinical evidence of documented polyuria and low USG. The presence of hypernatremia is supportive but not required to make the diagnosis. Pre-operative hormonal medications were also taken into consideration and was compared post-operatively as an indirect measurement of endocrine outcomes.

Post-operative complications such as diabetes insipidus, cerebrospinal fluid (CSF) leak, and post-operative meningitis were reported. Post-operative meningitis was diagnosed based on clinical presentation of fever, nuchal rigidity and altered mental status, in conjunction with CSF analysis, peripheral blood leukocytosis and response to meningitic doses of antibiotics.[11]

Statistical analyses were performed using STATA MP – Parallel Edition Statistical Software, Version 18 (StataCorp LP, TX, USA). A p-value ≤0.05 was considered statistically significant. Data normality was analyzed using Shapiro-Wilk's test. Descriptive statistics included mean and standard deviation (SD) for normally distributed, continuous data; median and interquartile range for ordinal data and non-normal, continuous data; and frequency and proportion for nominal data. Within-group comparisons of the different neurologic, ophthalmologic and endocrine outcomes from pre- to post-operative periods were conducted using McNemar's test for categorical variables; Wilcoxon signed-rank test for ordinal and non-normally distributed, continuous data; and paired t-test for normally distributed, continuous data. On the other hand, the associations of different factors with visual outcomes and change in hormonal changes were conducted using Cramer's V for nominal factors and eta correlation for continuous-level factors.[12]

RESULTS

All cases were acquired from a retrospective database from 2017 to 2022. A total of 188 patients with pituitary macroadenoma fulfilled the inclusion criteria, but 66 patients had missing charts and were excluded. Thus, only 122 patients were included in our sample. The baseline characteristics are summarized in Table 1. Multiple neurosurgeons performed the operations over the study period, mostly neurosurgery residents in training, although a few cases were performed by general and subspecialty consultant neurosurgeons. The level of expertise of the surgeon was not included in the variables analyzed, since they were mostly neurosurgery trainees and represented a relatively homogeneous group.

The mean age of the patients in our study was 44.18 years (SD ± 12.07), and majority (50.82%) were females. Nearly 40% had hypertension and 30% had diabetes mellitus. Most patients (77.87%) had non-functioning pituitary macroadenoma. Among those with functioning adenomas, the most prevalent was acromegaly (59.26%). The most common signs and symptoms overall were blurring of vision (59.02%) and headache (15.57%), while the most common symptom for functioning tumors was galactorrhea (15.57%).

The median maximum tumor diameter was 3.5 cm (IQR 3 to 4.3), with most tumors being 2.1 to 4 cm in maximum diameter (61.05%). Cavernous sinus involvement was seen in 28.38%, while hydrocephalus was present pre-operatively in 9.26% of patients.

Indications for surgery included visual compromise (68.85%), headache (15.37%), and functioning adenomas (10.66%). The most common surgical approach was microscopic transsphenoidal excision (TSE) (60.83%), followed by endoscopic TSE (24.17%) and transcranial excision (14.17%). Gross total tumor resection was achieved in 70.59%. The most common post-operative complications were transient DI (24.59%) and post-operative hematoma (4.92%), a third of which required reoperation (Table 2). The median length of hospital stay was 12 days (IQR 8 to 16). Nine patients (7.38%) underwent adjuvant radiotherapy for residual tumor.

Table 1. Demographic, clinical and radiographic characteristics of patients with pituitary macroadenoma

Characteristic	Frequency	Percentage (%)	Mean (SD[a]) or Median (IQR[b])
Age, years (SD[a])			44.18 (12.07)
Sex			
Male	60	49.18	
Female	62	50.82	
Comorbidities			
Hypertension	36	29.51	
Diabetes mellitus	25	20.49	
Cardiac disease	3	2.46	
Pulmonary disease	2	1.64	
Tumor size, cm (median, IQR[b], n = 95)			3.50 (3.00–4.30)
≤2.0	7	7.37	
2.1 to 4.0	58	61.05	
>4.0	30	31.58	
With cavernous sinus involvement (n = 74)	32	28.38	
With hydrocephalus (n = 108)	10	9.26	
Type of pituitary macroadenoma			
Non-functioning	95	77.87	
Functioning	27	22.13	
Acromegaly	16	59.26	
Prolactinoma	9	33.33	
Cushing's disease	1	3.70	
TSH-secreting	1	3.70	
Signs and symptoms			
Blurring of vision	72	59.02	
Headache	19	15.57	
Galactorrhea	19	15.57	
Visual field cuts	12	9.84	
Acromegalic features	9	7.38	
Amenorrhea	2	1.64	

[a] SD, standard deviation
[b] IQR, interquartile range

Table 2. Surgical indication, approach, extent of resection and post-operative complications of patients with pituitary macroadenoma

Characteristics	Frequency	Percentage (%)
Indications for surgery		
Visual compromise	84	68.85
Headache	19	15.37
Functioning adenoma	13	10.66
Treatment failure	9	7.38
Surgical approach (n=120)		
Transsphenoidal excision (microscopic)	73	60.83
Transsphenoidal excision (endoscopic)	29	24.17
Craniotomy for tumor excision	17	14.16
Ventriculoperitoneal shunt	1	0.83
Extent of resection (n=120)		
Gross total	84	70.59
Subtotal	35	29.41
Post-operative complications		
Transient diabetes insipidus	30	24.59
Post-operative hematoma	6	4.92
Meningitis	5	4.10
Cerebrospinal fluid leak	3	2.46
Pneumonia	3	2.46
Internal carotid artery injury	1	0.82

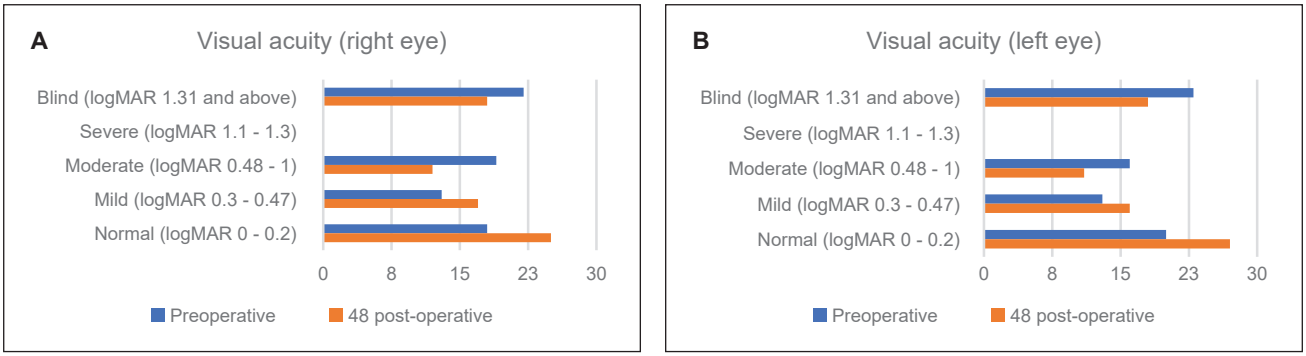

Figure 1. Pre-operative and 48-hour post-operative visual acuity [**(A)** right eye and **(B)** left eye] among patients with pituitary macroadenoma.

The median time from symptom onset to initial physician consult and neurosurgery consult were 2.96 months (IQR 0.00 to 12.00) and 12.00 months (IQR 4.44 to 35.86), respectively. Moreover, the interval from symptom onset to surgery was a median of 18.67 months (IQR 9.27 to 44.44). Majority of patients (31.25%) were seen by a neurosurgeon within 6 months of symptom onset, but most (27.35%) waited more than 3 years before they underwent surgery (Table 3).

Pre-operatively, the median Glasgow Coma Scale (GCS) score was 15. Only 5.15% of patients had neurological deficits, the most common of which was cranial nerve palsy (2.06%). Mean pre-operative visual acuities were 20/70, logMAR 0.54 (IQR 0.24 to 2.00) and 20/70, logMAR 0.54 (IQR 0.18 to 2.00) for the right and left eyes, respectively. Pre-operatively, 30.56% of patients were already blind (logMAR 1.31 and above) in the right eye, 31.94% in the left eye, and 2.78% bilaterally. Majority (60.56%) also exhibited bitemporal hemianopsia on confrontation test pre-operatively, while 16.90% had unilateral hemianopsia and 22.54% had normal visual fields.

Table 3. Descriptive statistics of the interval periods of events among patients with pituitary macroadenoma

Interval of events	Median (IQR[a])	Frequency	Percentage (%)
Symptom onset to initial physician consult (n=115)	2.96 (0.00-12.00)		
Less than 6 months		67	58.26
6 months to 1 year		22	19.13
1 to 2 years		7	6.09
2 to 3 years		6	5.22
More than 3 years		13	11.30
Symptom onset to neurosurgery consult (n=112)	12.00 (4.44-35.86)		
Less than 6 months		35	31.25
6 months to 1 year		24	21.43
1 to 2 years		16	14.29
2 to 3 years		14	12.50
More than 3 years		23	20.54
Symptom onset to surgery (n=117)	18.67 (9.27-44.41)		
Less than 6 months		16	13.68
6 months to 1 year		24	20.51
1 to 2 years		29	24.79
2 to 3 years		16	13.68
More than 3 years		32	27.35

[a] IQR, interquartile range

Of the 21.13% with functioning macroadenoma, acromegaly (59.26%) and prolactinoma (33.33%) were the most common. On the other end of the spectrum, 15.29% (13/85) had hypopituitarism, 22.09% (19/86) had hypocortisolism, 22.73% (25/110) had hypothyroidism, and 5.49% (5/91) had secondary hyperprolactinemia pre-operatively. One patient had pre-operative DI. The difference in the denominators was due to incomplete workup or missing information for some patients. Majority of patients with hypopituitarism were on levothyroxine (36.07%) and prednisone (22.13%).

Post-operatively, all patients remained GCS 15. Only 72 patients in our study had ophthalmologic data that could be compared pre- and post-operatively. After pituitary decompression surgery, the mean post-operative visual acuity was 0.40 logMAR (Snellen equivalent 20/50) for both eyes, from 0.54 logMAR (Snellen equivalent 20/70) pre-operatively. The improvement in the visual acuity scores for both eyes was statistically significant (p=0.001). In terms of visual fields, 60.56% reported subjective improvement; 38.03%, no change; and 1.41%, worsening.

Postoperative hormonal levels are described in Table 4 and Figure 2. Majority of patients with pituitary hypofunction did not exhibit any change in hormonal status from the pre-operative to the latest follow-up period. A smaller group of patients showed improvement in hypopituitarism (21.74%), hypothyroidism (19.35%) and hypocortisolism (8.33%). Data on hypogonadism was not estimated due to insufficient data. Proportions of patients who were on levothyroxine (36.07 vs. 17.21%, p = 0.001) and hydrocortisone (21.31 vs. 3.28%, p = 0.001) significantly decreased pre- and post-operatively. Initially, there were two time periods identified for follow-up: follow up number 1 (within 48 hours post-surgery) and number 2 (latest follow-up). Due to inconsistencies and lack of post-operative data including hormonal levels on follow up beyond the 48-hour period, results could not be properly accrued.

Correlation analyses of the different factors showed that age, sex, type of pituitary macroadenoma, size of tumor, timing of surgery, interval from symptom onset to surgery, surgical approach, post-operative complications and adju-

vant radiation therapy were not significantly associated with either the visual or endocrine outcomes of the patients (Appendices A and B). Outcomes associated with the level of expertise of the surgeons who performed each procedure were not analyzed and were deemed beyond the scope of the study.

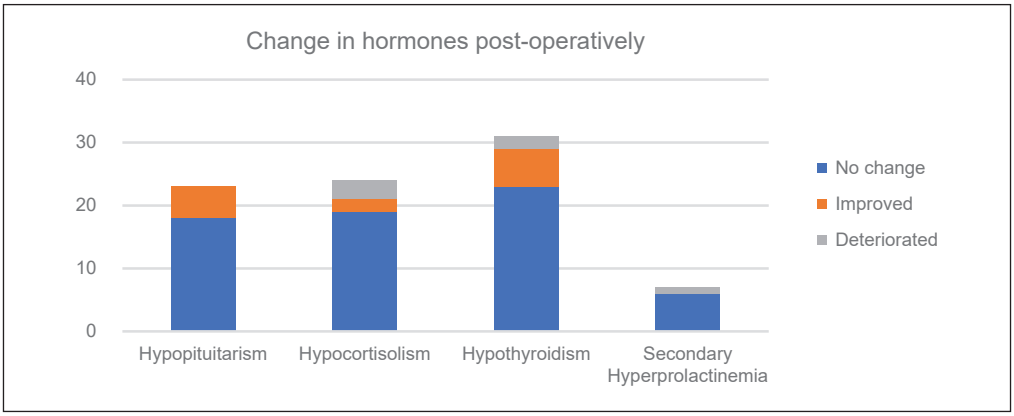

Figure 2. Post-operative hormonal status among patients with pituitary macroadenoma.

Table 4. Descriptive statistics of the neurologic, ophthalmologic, and endocrinologic outcomes of patients with pituitary macroadenoma

Outcome	Timeframe				*p*-value (two-tailed)
	Pre-operative		Latest Follow-up		
	n	Summary Statistic	n	Summary Statistic	
Neurologic outcomes					
Deficits, frequency (%)	97	5 (5.15)	40	3 (7.50)	0.625[a]
Palsy		2 (2.06)		1 (2.50)	1.000[a]
Paresis and plegia		1 (1.03)		1 (2.50)	1.000[a]
Ptosis		1 (1.03)		0	1.000[a]
Glasgow coma scale, median (IQR)	119	15 (15-15)	119	15 (15-15)	0.250[b]
Ophthalmologic outcomes					
Visual acuity (logMAR)					
Right eye	72	0.54 (0.18-2.00)	72	0.40 (0.10-1.15)	0.001[b]*
Normal (logMAR 0-0.2)		18 (25.00)		25 (34.72)	0.001[a]*
Mild (logMAR 0.3-0.47)		13 (18.06)		17 (23.61)	
Moderate (logMAR 0.48-1.0)		19 (26.39)		12 (16.67)	
Severe (logMAR 1.1-1.3)		0		0	
Blind (logMAR 1.31 and above)		22 (30.56)		18 (25.00)	
Left eye	72	0.54 (0.18-2.0)	72	0.40 (0.10-1.15)	0.001[b]*
Normal (logMAR 0-0.2)		20 (27.78)		27 (37.50)	0.001[a]*
Mild (logMAR 0.3-0.47)		13 (18.06)		16 (22.22)	
Moderate (logMAR 0.48-1.0)		16 (22.22)		11 (15.28)	
Severe (logMAR 1.1-1.3)		0		0	
Blind (logMAR 1.31 and above)		23 (31.94)		18 (25.00)	
Visual field cuts	71		–	–	–
Normal		16 (22.54)			
Unilateral		12 (16.90)			
Bilateral		43 (60.56)			
Blind		0			
Visual field cuts change	–	–	71		–
No change				27 (38.03)	
Improved				43 (60.56)	
Worsened				1 (1.41)	
Endocrine outcomes (%)					
Hormonal function					
Hypopituitarism	31	13 (15.29)		1 (3.12)	
Hypocortisolism	23	19 (22.09)		9 (28.12)	
Hypothyroidism	24	25 (22.73)		4 (11.43)	
Secondary hyperprolactinemia	7	5 (5.49)		2 (18.18)	
Medication					
Levothyroxine	122	44 (36.07)	122	21 (17.21)	0.001[a]*
Prednisone	122	27 (22.13)	122	21 (17.21)	0.334[a]*
Hydrocortisone	122	26 (21.31)	122	4 (3.28)	0.001[a]*
Metformin	122	2 (1.64)	122	5 (4.10)	0.250[a]*
Bromocriptine	122	5 (4.10)	122	2 (1.64)	0.250[a]*
Desmopressin	122	3 (2.46)	122	1 (0.82)	0.313[a]*
Medroxyprogesterone	0	–	122	1 (0.82)	0.316[a]*

Comparative analyses were conducted using the following:
[a] Chi-square test of homogeneity or Fisher's exact test
[b] Mann-Whitney U test
[c] Independent t-test

DISCUSSION

This is the first local in-depth study on the post-operative neurologic, ophthalmologic and endocrine outcomes of pituitary macroadenoma, as well as the delay from symptom onset to surgery.

Delay in diagnosis and treatment

Our study showed that it took three months for a patient to see a physician, 12 months to see a neurosurgeon and 18 months before they could undergo surgery. This supported the finding that timely diagnosis and universal access to treatment for pituitary adenoma patients remain difficult in our population. Contributing factors include the lack of specialists and equipment in local hospitals and the high cost of diagnostic examinations and treatment.[13] Waiting time for surgery differ according to country-level income, with high income countries (HICs) reporting an average wait time of four to 30 days, depending on the surgical urgency of each case.[14] Brain tumor patients tended to wait longer in LMICs than HICs, due to healthcare costs, lack of universal healthcare insurance programs, limited neurosurgery workforce, and lack of facilities such as operating rooms and hospital beds.[14]

Aside from socioeconomic factors, the benign nature of pituitary adenomas may have led to delay in diagnosis. Most of our patients presented with a large tumor size due to indolent growth and benign characteristics; hence, nearly one-third were already blind in one eye pre-operatively.[15] This finding was similar to the experience in Ghana, where 38.9% of patients were blind pre-operatively.[16] Furthermore, despite being one of the most common intracranial tumors, pituitary adenoma are fairly not known by the general public.[17] Since the patients' presenting symptoms were mainly visual problems, their first consult would be with ophthalmology, contributing to delay in surgical treatment.[17]

Timing of surgery and surgical approach

Almost one-third of our patients underwent surgery more than three years from symptom onset, but our results showed that the timing of surgery had no significant association with visual and endocrine outcomes. This was in contrast to a study that reported that the duration and severity of pre-operative visual symptoms may dictate the post-operative outcome; hence, the dictum is to treat early to preserve and correct visual deficits.[2,16] A meta-analysis found that symptom duration was one of the predictive factors affecting visual recovery after surgery, while other studies reported inconsistent results.[8,18] In our cohort, several of our patients were already blind pre-operatively, which may have affected the analysis.

Surgery is the mainstay treatment for pituitary macroadenoma, and endoscopic transsphenoidal excision (TSE) has been the technique of choice in most centers internationally since it was introduced more than 20 years ago.[16] Furthermore, surgery is indicated in patients with functioning pituitary macroadenoma who are refractory to medical treatment. In a meta-analysis comparing microscopic and endoscopic TSE, the endoscopic arm showed higher gross total resection rates and visual recovery among patients.[19] In our cohort, microscopic TSE was performed more than twice as often as endoscopic TSE. This was due to the lack of equipment and specialists that only became available fairly recently in our center.

Post-operative outcomes

Ophthalmologic

There was a statistically significant improvement of approximately one line of visual acuity in our patients post-operatively. Most patients also demonstrated subjective improvement in their visual field. This phenomenon was due to the biological response of the optic nerve to decompression during surgery, which may take place within ten minutes of decompression.[6,20]

The pattern of visual field defect depends on the growth pattern of the tumor.[21] Compression of the optic chiasm produces visual pathology directly due to its mass effect upon the axons, impairing axonal transport and signal transmission. It may also produce pathology indirectly through the compression of perivascular structures that supply the chiasm, producing ischemia. In animal models, chronic nerve compression has demonstrated a direct dose-response relationship, in which the duration of compression correlated with the degree of nerve injury. Histopathologic evidence demonstrated initial breakdown of the blood-nerve barrier, followed by perineural edema and subsequent gliosis. With loss of trophic stimuli, diffuse demyelination was then observed, with subsequent Wallerian degeneration.[22]

This retrograde degeneration of axons from the optic chiasm was directly observed during funduscopic examination as optic atrophy. Objective measurement of the retinal nerve fiber layer (RNFL) thickness through OCT has been found to demonstrate prognostic value for immediate visual recovery after pituitary decompression.[23] Patients with a RNFL thickness of ≥80 microns were found to have greater visual recovery post-operatively compared to those with thinner RNFL at presentation.[24]

Visual recovery was postulated to be divided into three phases: rapid recovery (within minutes to one week post-operatively), early slow phase (one to four months) where improvement was more evident, and late phase (six months to three years) where there was only minimal improvement.[6] Clinical studies reported progressive improvement in visual acuity, which usually ranged from one to two years and even as late as five years post-operatively.[6,16,25] For visual field recovery, most of the improvement occurred within three to six months after surgery.[26] Other authors observed that the majority of visual improvement occurred within

the first six to ten weeks, with continued improvement up to one year post-operatively. Immediate improvement occurs due to the removal of the physiologic conduction block,[6,27] and visual evoked responses were documented to improve as early as 10 minutes after surgical pituitary decompression.[20] Over time, limited remyelination and resumption of axoplasmic flow may produce guarded visual recovery.[6,27] Our study adds to the current neuro-ophthalmologic evidence that pituitary decompression surgery may still demonstrate potential visual benefit.

Endocrine

The incidence of individual endocrine deficits in our study was consistent with that reported in the local literature, where adrenal insufficiency (22.09%) and hypothyroidism (22.73%) were found to be the most common endocrinopathies, followed by secondary hyperprolactinemia (19.35%).[28] However, the lack of routine assessment of growth hormone (GH) and luteinizing hormone/follicle-stimulating hormone (LH/FSH) axes in all patients at admission prevented accurate estimate of GH deficit and hypogonadism. Since we did not have complete data about the patients' hormonal status, the use of hormone replacement therapy was used as an indirect way to assess the improvement of the endocrine axis among our patients post-operatively. The study demonstrated significant decrease in use of levothyroxine and hydrocortisone/prednisone among patients who underwent surgery, which suggested resolution of hormonal deficiencies.

After uneventful surgery, pituitary function is usually evaluated four to six weeks post-operatively, since earlier evaluation may falsely reflect the hormonal status.[29] Jahangiri et al., reported that the three anterior pituitary axes (hypogonadism, hypothyroidism, and hyposomatotropism) showed delayed normalization of laboratory values, occurring between six weeks to six months.[30] Hence, our findings that 74-85% of our patients exhibited persistent pituitary hypofunction post-operatively may be overestimated due to poor patient follow-up.

However, pre-operative hypopituitarism was unlikely to be corrected with surgery.[31] This may be due to the destructive effect of tumor compression on the pituitary gland or from the disturbance in the portal circulation which causes ischemic processes and cell necrosis, leading to pituitary hypofunction.[30] Similar to the compressive effect of pituitary tumors on the optic nerve and subsequent visual outcomes, longstanding tumors may lead to limited endocrine recovery because the pituitary gland has little capacity for regeneration.[31] This was consistent with our findings; majority of our patients did not show any endocrine improvement post-operatively. Younger age, absence of hypertension, and absence of intra-operative CSF leak were identified as the strongest clinical predictors of hormonal recovery.[32] Tumor size and baseline pituitary gland volume were also thought to affect the recovery of hypopituitarism after surgery,[32] but other authors reported that there was no significant association.[33]

Functioning adenoma comprises 22% of the total population in the study with prolactinoma and acromegaly as the most common hypersecreting pituitary tumors. Although medical management has been previously the treatment of choice for prolactinoma, this study reflects increasing utilization of surgery for this subgroup. Treatment with bromocriptine or cabergoline showed remission rate of 90% with microprolactinoma and 70% with macroprolactinoma.[34] For those patients who underwent surgical resection of prolactinoma, the cure rate was at 70% among microprolactinomas, and only 30% among macroprolactinomas, especially if the cavernous sinus is involved.[35] Prolactin levels are closely followed up for the first year after surgery, and increasing levels suggest tumor recurrence, or tumor progression in cases of residual tumor.[35] Outcomes of prolactinoma patients who underwent surgery were not demonstrated due to insufficient data on post operative hormonal levels among the patients included. However, indirect measures such as the use of dopamine agonist therapy were remarkably decreased among these post-operative patients.

Acromegaly, on the other hand, was one of the most common hypersecreting pituitary tumors in our study. Trial of medical therapy has been the first line treatment for acromegaly, especially in cases with only moderate clinical symptoms. Medical treatment include somatostatin analogue, pegvisomant, and dopamine agonist such as cabergoline, in cases of modest biochemical abnormality and minimal metabolic symptoms.[35] In our experience, medical treatment can be challenging due to its unsustainable cost among patients.[13] In fact, our data showed that none of the acromegalic patients were able to start any of the first line medical treatment, and instead, all of which opted to undergo surgical resection as this was more feasible rather than the hormonal treatment available.

Acromegalic patients who underwent surgical tumor resection would have immediate improvement in metabolic parameters within hours of resection.[35] With insufficient data on post-operative hormonal levels among our patients, an accurate measurement of outcomes among this subset of patients were unlikely.

Surgical complications and length of hospital stay

Transient DI was the most common complication in our cohort, similar to other studies but in contrast to others, wherein CSF leak was the most common.[34,36,37] The incidence of transient DI in our study (24.59%) was slightly higher compared to other centers, which ranged from 18.3% to 24%.[1,32,38] These results may be confounded by the retrospective nature of some studies, as well as the surgical technique and experience of the surgeons involved.[36] It was also reported that patients who had CSF leak intra-operatively had a higher risk of transient DI post-operatively due to more aggressive resection.[38] Fortunately, the rate of permanent DI is low, ranging from 0-2%.[30,32,38]

The most common type of complication influenced the median length of hospital stay (12 days), since patients who developed transient DI had to stay longer for serial monitoring of serum sodium, urine output, and urine specific gravity. Our length of stay was slightly longer than the median of five to eight days after uneventful surgery in most centers.[39] Stratified fast-track care in pituitary surgery was also being explored. Patients were discharged two to three days after uneventful surgery and followed up regularly at home by a case manager, decreasing overall costs.[40]

Follow up

Poor patient follow-up and inconsistencies with pre- and post-operative outcome measures were evident in our study. In fact, 36% of the initial cohort were excluded due to incomplete charts. Geographic and socioeconomic factors likely played a role in the poor follow-up. Since the country is an archipelago, patients may find it challenging to seek medical consult due to transportation difficulties, especially those in isolated rural areas.[13] They would also have to shoulder the cost of transportation, adding to the cost of medical care.

The latter part of the study period coincided with the coronavirus-19 (COVID-19) pandemic which resulted in lockdowns, travel restrictions, and closure of non-urgent services such as the outpatient department. Even after the telemedicine service was implemented, patient follow-up was still very poor. For the pituitary adenoma patients who were able to participate in telemedicine, there was an incomplete assessment of neurological and visual outcomes due to the inability of physicians to examine patients face-to-face.

Another sequela of the pandemic was the rapid transition to electronic medical records in our institution. This process may have contributed to the incomplete data on post-operative outcomes in our study, particularly in the years 2020 to 2021, due to clinicians' inexperience with the new platform and intrinsic errors in the new system.

Due to the retrospective design of our study, there was no regular follow-up interval aside from the first 48 hours post-operatively. A systematic review on the topic showed that there was heterogeneity in the length of follow-up across studies due to income level, availability of resources, and the multidisciplinary nature of the disease. In fact, the authors highlighted that lost patient data might have been a more common problem than a patient being lost to follow-up, hence they suggested a more centralized and standardized method in evaluating outcomes following treatment.[39] As for the timing of post-operative imaging, there is no standard at present. Kunigelis et al.,g suggested performing cranial imaging at least three months post-operatively, since earlier scans were equivocal and resulted in increased reoperation rates but did not show any difference in the long-term clinical outcomes.[41]

Recommendations

We recommend establishing a centralized patient database that could be accessed by the different specialty services in the multidisciplinary pituitary team. This will include uniform pre- and post-operative neurologic, ophthalmologic and endocrine assessments in order to accurately compare and quantify the outcomes of our patients. Pre- and post-operative diagnostic examinations (automated visual perimetry, OCT and hormonal workup) should be standardized. A uniform follow-up schedule should also be implemented to facilitate comparison of visual and endocrine changes pre- and post-operatively.

Limitations

The limitations of our study included the following: it was retrospective in nature, involved only a single center, and had incomplete data due to missing charts. In addition, we may have overlooked any potential significance in the correlational analysis due to missing charts and inconsistent post-operative data.

CONCLUSION

This is the first local study to comprehensively assess the entirety of post-operative outcomes among pituitary macroadenoma patients. Our results showed that the median tumor size was 3.5 cm and the median time to surgery was 18 months. Despite these, there was subjective improvement in the patients' visual fields, and the mean visual acuity improved by approximately one line in the Snellen chart post-operatively. There was also some improvement in endocrine function post-operatively. This showed that even patients with longstanding visual and endocrine deficits may still improve with surgery. Improvements are needed to decrease surgical delays, achieve better post-operative outcomes, encourage patient follow-up and standardize pre- and post-operative treatment protocols.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
MUH: Conceptualization, Resource, Data Curation, Writing – original draft preparation, Writing – review and editing; **DJL and JAN:** Conceptualization, Resource, Data Curation, Writing – original draft preparation, Writing – review and editing; **KSS:** Writing – review and editing, Supervision, Project administration. **KOK:** Conceptualization, Writing – original draft preparation, Writing – review and editing, Supervision, Project Administration.

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APPENDICES

Appendix A. Correlation analyses of the association of the different factors with the visual outcome among patients with pituitary macroadenoma (N = 122)

Characteristic	Visual acuity change										Visual field cut change				
	Right Eye					Left Eye									
	N	No change	Improved	Worsened	*p*-value	N	No change	Improved	Worsened	*p*-value	N	No change	Improved	Worsened	*p*-value
Age, year	72	42.38 (10.72)	47.5 (15.81)	45.33 (12.82)	0.535	72	43.25 (11.69)	48.0 (11.78)	43.22 (11.85)	0.656	71	45.15 (14.89)	44.26 (10.46)	31.0 (0)	0.530
Sex (%)	72				0.382	72				0.067	71				0.571
Male		18 (40.91)	14 (8.33)	2 (50.0)			25 (58.14)	8 (34.78)	1 (16.67)			13 (48.15)	23 (53.49)	1 (100)	
Female		26 (59.09)	10 (41.67)	2 (50.0)			18 (41.86)	15 (65.22)	5 (83.33)			14 (51.85)	20 (46.51)	0	
Macroadenoma type				4 (100.0)	0.002*										
Non-functioning	72	30 (16.18)	24 (100.0)			72	34 (79.07)	19 (82.61)	5 (83.33)	1.000	71	19 (70.37)	38 (88.37)	1 (100.0)	0.148
Functioning		14 (31.82)	0				9 (20.93)	4 (17.39)	1 (16.67)		71	8 (29.63)	5 (11.63)	0	
Acromegaly	72	9 (20.45)	0			72	8 (18.6)	1 (4.35)	0	0.227	71	7 (25.93)	3 (6.98)	0	0.079
Prolactinoma	72	4 (9.09)	0			72	0	3 (13.04)	1 (16.67)	0.024*	71	0	2 (4.65)	0	0.512
Cushing's disease	72	1 (2.27)	0			72	1 (2.33)	0	0	1.000	71	1 (3.7)	0	0	0.438
TSH-secreting	72	0	0			72	0	0	0	-	71	0	0	0	-
Tumor size (%)	62				0.862	62				0.973	65				0.063
≤2 cm		2 (5.41)	0	1 (4.55)			2 (5.13)	0	1 (5.0)			4 (17.39)	0	0	
2.1 to 4.0 cm		23 (62.16)	3 (100.0)	15 (68.18)			23 (63.89)	4 (66.67)	14 (70.0)			11 (47.83)	28 (68.29)	1 (100.0)	
>4.0 cm		12 (32.43)	0	6 (27.27)			11 (30.56)	2 (33.33)	5 (25.0)			8 (34.78)	13 (31.71)	0	
Timing of surgery	72				0.176	72				0.229	71				0.120
<6 months		6 (13.64)	4 (16.67)	1 (25.0)			8 (18.6)	3 (13.04)	0			4 (14.81)	3 (6.98)	1 (100.0)	
6 months to 1 year		9 (20.45)	3 (12.5)	1 (25.0			7 (16.28)	5 (21.74)	1 (16.67)			3 (11.11)	7 (16.28)	0	
1 to 2 years		10 (22.73)	6 (25.0)	0			10 (23.26)	6 (26.09)	0			5 (18.52)	10 (23.26)	0	
2 to 3 years		3 (6.82)	7 (29.17)	1 (25.0)			5 (11.63)	2 (8.7)	4 (66.67)			3 (11.11)	8 (18.6)	0	
>3 years		16 (36.36)	4 (16.67)	1 (25.0)			13 (30.23)	7 (30.43)	1 (16.67)			12 (44.44)	15 (34.88)	0	
Symptom onset to initial consult	67				0.659	67				0.336	67				0.574
<6 months		20 (48.78)	10 (45.45)	2 (50.0)			16 (40.0)	13 (61.9)	3 (50.0)			9 (33.33)	18 (47.37)	1 (100.0)	
6 months to 1 year		11 (26.83)	5 (22.73)	0			11 (27.5)	5 (23.81)	0			9 (33.33)	8 (21.05)	0	
1 to 2 years		4 (9.76)	2 (9.09)	1 (25.0)			4 (10.0)	2 (9.52)	1 (16.67)			1 (3.7)	6 (15.79)	0	
2 to 3 years		2 (4.88)	1 (4.55)	1 (25.0)			4 (10.0)	0	0			3 (11.11)	2 (5.26)	0	
>3 years		4 (9.76)	4 (18.18)	0			5 (12.5)	1 (4.76)	2 (33.33)			5 (18.52)	4 (10.53)	0	
Symptom onset to neurosurgery consult	67				0.088	67				0.878	64				0.187
<6 months		13 (31.71)	5 (22.73)	0			10 (24.39)	7 (35.0)	1 (16.67)			4 (16.0	11 (28.95)	1 (100.0)	
6 months to 1 year		9 (21.95)	6 (27.27)	1 (25.0)			10 (24.39)	4 (20.0)	2 (33.33)			6 (24.0)	9 (23.68)	0	
1 to 2 years		5 (12.2)	5 (22.73)	0			7 (17.07)	2 (10.0)	1 (16.67)			3 (12.0)	6 (15.79)	0	
2 to 3 years		3 (7.32)	1 (4.55)	3 (75.0)			6 (14.63)	1 (5.0)	0			7 (28.0)	2 (5.26)	0	
>3 years		11 (26.83)	5 (22.73)	0			8 (19.51)	6 (30.0)	2 (33.33)			5 (20.0)	10 (26.32)	0	
Surgical approach	71				0.447	71				0.044*	70				0.836
TSE[a] (microscopic)		26 (59.09)	11 (47.83)	1 (25.0)			24 (57.14)	13 (56.52)	1 (16.67)			14 (51.85)	20 (47.62)	0	
TSE[a] (endoscopic)		13 (29.55)	10 (43.48)	2 (50.0)			16 (38.1)	7 (30.43)	2 (33.330			9 (33.33)	16 (38.1)	1 (100.0)	
Craniotomy		5 (11.36)	2 (8.7)	1 (25.0)			2 (4.76)	3 (13.04)	3 (50.0)			4 (14.81)	6 (14.29)	0	
Post-operative complications															
CSF[b] leak	72	1 (2.27)	2 (8.33)	0	0.397	72	2 (4.65)	1 (4.35)	0	1.000	71	1 (3.7)	0	2 (4.65)	1.000
Hematoma	72	1 (2.27)	0	0	1.000	72	1 (2.33)	0	0	1.000	71	3 (11.11)	0	0	0.093
Transient DI[c]	72	13 (29.55)	7 (29.17)	1 (25.0)	1.000	72	12 (27.91)	7 (30.43)	2 (33.33)	1.000	71	5 (18.52)	15 (34.88)	0	0.293
Meningitis	72	4 (9.09)	0	0	0.437	72	4 (9.3)	0	0	0.381	71	1 (3.7)	0	3 (6.98)	1.000
Adjuvant radiation therapy	36	5 (21.74)	2 (16.67)	0	1.000	36	4 (15.38)	2 (25.0)	1 (50.0)	0.433	35	1 (7.69)	0	5 (22.73)	0.377

Note: Analysis for ventriculoperitoneal shunt (surgical approach), internal carotid artery injury (post-operative complications), permanent diabetes insipidus (post-operative complications), and pneumonia (post-operative complications) were not feasible due to insufficient cases.

Analyses were conducted using the following: Eta Correlation, Cramer V

* Significant at 0.05

[a] TSE, transsphenoidal excision; CSF, cerebrospinal fluid; [c] DI, diabetes insipidus

Appendix B. Correlation analyses of the association of the different factors with the endocrine outcome among patients with pituitary macroadenoma (n = 122)

Characteristic	Change in hormonal level														
	Hypopituitarism					Hypocortisolism					Hypothyroidism				
	N	No change	Improved	Worsened	*p*-value	N	No change	Improved	Worsened	*p*-value	N	No change	Improved	Worsened	*p*-value
Age, year[a]	23	40.06 (11.89)	45.0 (10.8)	44.89 (12.13)	0.412	24	41.0 (1.26)	43.0 (8.49)	43.33 (8.74)	0.923	31	40.87 (10.78)	44.17 (7.36)	39.5 (7.78)	0.751
Sex (%)	23				0.280	24				0.333	31				0.609
Male		6 (33.33)	3 (60.0)	0			8 (42.11)	0	2 (66.67)			7 (30.43)	3 (50.0)	1 (50.0)	
Female		12 (66.67)	2 (40.0)	0			11 (57.89)	2 (100.0)	1 (33.33)			16 (69.57)	3 (50.0)	1 (50.0)	
Macroadenoma type[b]															
Non-functioning	23	11 (61.11)	2 (100.0)	3 (100.0)	0.095	24	11 (57.89)	2 (100.0)	3 (100.0)	0.206	31	14 (60.87)	5 (83.33)	1 (50.0)	0.536
Functioning		7 (38.89)	0	0			8 (42.11)	0	0			9 (39.13)	1 (16.67)	1 (50.0)	
Acromegaly	23	3 (16.67)	0	0	0.328	24	4 (21.05)	0	0	0.532	31	5 (21.74)	0	1 (50.50	0.256
Prolactinoma	23	2 (11.11)	0	0	0.435	24	2 (10.53)	0	0	0.750	31	2 (8.70)	1 (16.67)	0	0.750
Cushing's disease	23	1 (5.56)	0	0	0.590	24	1 (5.26)	0	0	0.872	31	1 (4.35)	0	0	0.836
TSH-secreting	23	1 (5.56)	0	0	0.590	24	1 (5.26)	0	0	0.872	31	1 (4.35)	0	0	0.836
Tumor size (%)	20				0.211	21				0.768	27				0.138
≤2 cm		2 (11.76)	0	0			2 (11.76)	0	0			2 (9.52)	0	1 (50.0)	
2.1 to 4.0 cm		0	0	0			0	0	0			1 (4.76)	0	0	
>4.0 cm		15 (88.24)	2 (100.0)	3 (100.0)			15 (88.24)	2 (100.0)	3 (100.0)			18 (85.71)	5 (100.0)	1 (50.0)	
Timing of surgery (%)[b]	23				0.120	24				0.047*	31				0.083
<6 months		4 (22.22)	0	0			2 (10.53)	0	2 (66.67)			4 (17.39)	1 (16.67)	0	
6 months to 1 year		1 (5.56)	2 (40.0)	0			2 (10.53)	1 (50.0)	0			1 (4.35)	3 (50.0)	0	
1 to 2 years		6 (33.33)	2 (40.0)	0			8 (42.11)	0	0			4 (17.39)	2 (33.33)	1 (50.0)	
2 to 3 years		1 (5.56)	1 (20.0)	0			1 (5.26)	1 (50.0)	1 (33.33)			6 (26.09)	0	0	
>3 years		6 (33.33)	0	0			6 (31.58)	0	0			8 (34.78)			
Symptom onset to initial consult (%)[b]	22				0.249	23				0.245	30				0.546
<6 months			9 (52.94)	3 (60.0			12 (66.67)	1 (50.0)	1 (33.33)			11 (50.0)	4 (66.67)	2 (100.0)	
6 months to 1 year			4 (23.53)	0			4 (22.22)	0	0			7 (31.82)	0	0	
1 to 2 years			2 (11.76)	0			1 (5.56)	0	1 (33.33)			1 (4.55)	1 (16.67)	0	
2 to 3 years			1 (5.88)	0			0	0	0			0	0	0	
>3 years			1 (5.88)	2 (40.0)			1 (5.56)	1 (50.0)	1 (33.33)			3 (13.64)	1 (16.67)	0	
Symptom onset to neurosurgery consult (%)[b]	21				0.380	22				0.716	29				0.119
<6 months		6 (35.29)	1 (50.0)	0			6 (35.29)	1 (50.0)	0			2 (9.52)	4 (66.67)	1 (50.0)	
6 months to 1 year		5 (29.41)	0	1 (33.33)			5 (29.41)	0	1 (33.33)			9 42.86)	0	0	
1 to 2 years		2 (11.76)	0	0			2 (11.76)	0	0			3 (14.29)	0	0	
2 to 3 years		1 (5.88)	0	0			1 (5.88)	0	0			2 (9.52)	0	0	
>3 years		3 (17.65)	1 (50.0)	2 (66.67)			3 (17.65)	1 (50.0)	2 (66.67)			5 (23.81)	2 (33.33)	1 (50.0)	
Surgical approach (%)[b]	23				0.305	24				0.156	31				0.710
TSE[c] (microscopic)		10 (55.56)	1 (20.0)	0			9 (47.37)	1 (50.0)	2 (66.67)			15 (65.22)	4 (66.67)	2 (100.0)	
TSE[c] (endoscopic)		7 (38.89)	3 (60.0)	0			9 (47.37)	0	0			5 (21.74)	2 (33.33)	0	
Craniotomy		1 (5.56)	1 (20.0)	0			1 (5.26)	1 (50.0)	1 (33.33)			3 (13.04)	0	0	
Post-operative complications (%)[b]															
CSF[d] leak	23	1 (5.56)	0	2 (2.02)	0.590	24	1 (5.26)	0	0	0.872	31	2 (8.70)	0	0	0.689
Hematoma	23	0	0	0	-	24	0	0	0	-	31	0	0	0	-
Transient DI[e]	23	4 (22.22)	1 (20.0)	0	0.915	24	5 (26.32)	0	1 (33.33)	0.762	31	6 (26.09)	2 (33.33)	1 (50.)	0.749
Meningitis	23	1 (5.56)	0	0	0.590	24	1 (5.26)	0	0	0.872	31	0	0	0	-
Adjuvant radiation therapy	18	1 (7.69)	2 (40.0)	0	0.099	18	3 (21.43)	1 (50.0)	0	0.480	2	4 (26.67)	1 (25.0)	0	0.837

Note: Analysis for ventriculoperitoneal shunt (surgical approach), internal carotid artery injury (post-operative complications), permanent diabetes insipidus (post-operative complications), and pneumonia (post-operative complications) were not feasible due to insufficient cases.

* Significant at 0.05

Analyses were conducted using the following: [a] Eta Correlation; [b] Cramer V

[c] TSE, transsphenoidal excision; [d] CSF, cerebrospinal fluid; [e] DI, diabetes insipidus