RETROSPECTIVE ANALYSIS OF OUTCOMES FOLLOWING ENDOSCOPIC ENDONASAL SURGERY FOR PITUITARY ADENOMA IN ELDERLY POPULATION (> 60 YEARS) IN COMPARISON TO A YOUNGER COHORT (45-60 YEARS)

Dr Arun Gowda K

MCh THESIS

2022

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY TRIVANDRUM

An Institution of National Importance established by an Act of the Indian Parliament (Act No.52 of 1980)

Dept. of Science and Technology, Govt. of India
www.sctimst.ac.in

RETROSPECTIVE ANALYSIS OF OUTCOMES FOLLOWING ENDOSCOPIC ENDONASAL SURGERY FOR PITUITARY ADENOMA IN ELDERLY POPULATION (> 60 YEARS) IN COMPARISON TO A YOUNGER COHORT (45-60 YEARS)

A THESIS SUBMITTED BY

Dr Arun Gowda K

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

MCh NEUROSURGERY

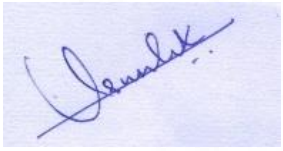
2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, **Dr Arun Gowda K** hereby certify that I had personally carried out the work depicted in the thesis titled, "**RETROSPECTIVE ANALYSIS OF OUTCOMES FOLLOWING ENDOSCOPIC ENDONASAL SURGERY FOR PITUITARY ADENOMA IN ELDERLY POPULATION (> 60 YEARS) IN COMPARISON TO A YOUNGER COHORT (45-60 YEARS)**"

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



Signature

Dr Arun Gowda K

Date: 27/7/2022

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: Dr Easwer HV

Department: Neurosurgery

This is to certify that Dr Arun Gowda K, Department of Neurosurgery of this institute has fulfilled the requirements prescribed for the MCh Neurosurgery degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, "***Retrospective analysis of outcomes following endoscopic endonasal surgery for pituitary adenoma in elderly population (> 60 years) in comparison to a younger cohort (45-60 years)***" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee of this institute for carrying out the study.

Signature

Date: 28-7-2022

Dr. EASWER H.V.
Professor & Head
Dept. of Neurosurgery
SCTIMST, Thiruvananthapuram

Dr Easwer HV,
Professor and Head
Department of Neurosurgery,
SCTIMST, Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the Co-Guide: Dr Prakash Nair

Department: Neurosurgery

This is to certify that Dr Arun Gowda K, Department of Neurosurgery of this institute has fulfilled the requirements prescribed for the MCh Neurosurgery degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The work under the thesis entitled, "***Retrospective analysis of outcomes following endoscopic endonasal surgery for pituitary adenoma in elderly population (> 60 years) in comparison to a younger cohort (45-60 years)***" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Signature

Date: 27.07.2022

Dr Prakash Nair
Associate Professor,
Department of Neurosurgery,
SCTIMST, Trivandrum

Dr. PRAKASH NAIR
MS (General Surgery), MCh (Neurosurgery)
Associate Professor
Department of Neurosurgery
Sree Chitra Tirunal Institute for
Medical Sciences & Technology
Thiruvananthapuram, Kerala, India
TCMC Reg. No. 38394

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

APPROVAL OF THE THESIS

The thesis entitled

Retrospective analysis of outcomes following endoscopic endonasal surgery for pituitary adenoma in elderly population (> 60 years) in comparison to a younger cohort (45-60 years)

Submitted by

Dr Arun Gowda K

for the degree of

MCh NEUROSURGERY(AFTER MS)

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

is evaluated and approved by

..... Dr. EASWER H.V.
Professor & Head
Dept. of Neurosurgery
SCTIMST, Thiruvananthapuram

(Name & Signature of the Guide)

.....

(Name & Signature of thesis examiner)

ACKNOWLEDGEMENTS

I thank almighty for giving me the strength and courage to endure through this. Throughout this period, I have received immense support from a great deal of people without which my dissertation would not have reached the present stage. I would like to thank my esteemed institution, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) for giving me such a great opportunity to pursue with my thesis.

I would like to thank Dr. Easwer H. V, Professor and Head of the Department of Neurosurgery, my guide whose support had been invaluable. I am eternally grateful and indebted for his contributions and suggestions, which were of crucial help during the entire work.

I'm extremely grateful to Dr. Prakash Nair, Additional Professor, Department of Neurosurgery, SCTIMST, my co-guide whose support had been invaluable, I am eternally grateful and indebted for his contributions and suggestions, which were of crucial help during the entire work. who was always there to clear my doubts and help me with the writing of this work.

I am deeply indebted to Dr. Mathew Abraham, Dr. Krishnakumar K, Dr. George C Vilanilam, Dr. Jayanand B Sudhir, Dr Tobin George, Dr. Ganesh Divakar. I thank them for their constant encouragement and support.

I am very grateful to my seniors Dr Gohil Jaypalsinh Ashoksigh, Dr Gowtham M and my batchmate Dr Darshan H R for their immense help in collecting robust data.

I am very thankful to Dr Antony Stanley, Research Associate, Regional Technical Resource Centre for Health Technology Assessment, AMCHSS, SCTIMST, for all the statistical analysis work, which were of crucial help during the entire work.

I am very grateful to my family especially my wife Dr. Nischitha Arun, for their constant encouragement and moral support.

I am very grateful to my colleagues and seniors Dr Amjad Jamaluddin, Dr Biren Patel, Dr Ninad Sawant, Dr Shrey Shah, Dr Sanjay H M, Dr Harshavardhan Biradar, Dr Arvind Singh, Dr Ajith Singh, Dr Sreenath P R, Dr Anand Binu, Dr Sam Scaria, Dr Akhilesh Gowda, Dr Lokesh V D, Dr Akhade Bhushan Sadashiv, Dr Suraj Gopal, Dr Parapati Vamshi Reddy, Dr Ram Kishan, Dr Ashutosh Carpenter and Dr Pooja Choudhary for their constant encouragement and moral support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1.	PA	Pituitary adenoma
2.	DI	Diabetes Insipidus
3.	ASA	American Society of Anaesthesiology.
4.	FI	Frailty index
5.	CCI	Charlson Comorbidity Index score
6.	BMI	Body Mass Index
7.	CSF	Cerebrospinal Fluid
8.	ICA	Internal Carotid Aretry
9.	SSPS	Statistical package for the social sciences
10.	SD	Standard Deviation
11.	VA	Visual Acuity
12.	VF	Visual Field
13.	NFPA	Non-Functioning Pituitary Adenoma
14.	WHO	World Health Organization
15.	EOR	Extent of resection
16.	POD	Post operative day
17.	DM	Diabetes mellitus,

18.	HTN	Hypertension
19.	CAD	Coronary artery disease
20.	IVH	Intraventricular haemorrhage
21.	ARF	acute renal failure
22.	AWMI	Anterior wall myocardial infarction
23	NA	Not applicable

ABSTRACT

OBJECTIVE: 1.To determine the factors responsible for post-operative visual, hormonal and surgical outcomes in elderly patients (>60 years) who underwent endoscopic transnasal approach for pituitary adenoma (PA). 2.Comparison of surgical outcomes in patients aged > 60 years to a younger cohort of patients (age 45-60 years) and to evaluate the factors that determine the risk of developing morbidity and mortality in the elderly population.

METHODS: This was a retrospective study where patients with diagnosed PA above 45 years and underwent endoscopic endonasal resection of pituitary adenoma between year 2009 to 2021 were included. Demographic data of each patient including age, sex, comorbidities, pre and postoperative visual & hormonal status, tumor size, extent of resection, duration of hospital stay, surgical outcomes, complications and follow up at 3weeks, 3months and 1 year were collected from EMR available in institute. The data was analysed using SPSS software (IBM SPSS Statistics for windows, version 23.0(Armonk, NY:IBM Corp).

RESULTS: A total of 361 patients above the age of 45 years were included in the study. Group 1 comprising of patients between 45-60 years included 269 (females-144, males- 125) and the group 2 comprising of patients ages > 60 years included 92 patients (females- 43, males- 49). The mean Charlson comorbidity score for group 1 was 3.071(SD 1.074) and for group 2 was 4.8(SD 1.19) ($p<0.001$). The preoperative Charlson comorbidity score showed strong correlation with the ASA grade ($p<0.001$). Visual acuity disturbances were present in 83.3% group 1 patients and 92.4% group 2 patients ($p=0.032$). Visual field deficits were seen in 89.1% of patients in group 2 as compared to 78.8% of group 1 patients ($p=0.028$). The higher incidence of preoperative visual field defects were seen in patients with a higher Charlson comorbidity score of 5-6 (92.6%) and > 6 (92.9%)($p=0.002$). The incidence of hemiparesis and cranial nerve palsies (4.7%, $p=0.027$) at presentation was also seen in patients with a higher Charlson comorbidity score. The incidence of intraoperative CSF leak was

greater in patients with a higher Charlson comorbidity score (p=0.046). The incidence of post operative CSF rhinorrhoea for group 1 was 16.7% and for group 2 was 14.1%(p=0.558). The incidence of post-operative Diabetes Insipidus (DI) for group 1 was 17.8% and group 2 was 20.7% (p=0.395).

CONCLUSION: Our study suggests that surgery should be the first line of treatment for non-functioning pituitary macroadenomas in the elderly. Patients should be selected for surgical treatment based on their symptoms and clinical condition. Age alone does not determine, rather associated comorbidities and frailty of the patient at the time of surgery which determines surgical outcome and associated perioperative morbidity and mortality. Hence endoscopic transnasal excision is a safe treatment modality among patients with pituitary adenoma up to eighth decade of life. ASA grade, Charlson's comorbidity index score and frailty index are an important prognosticating factors in determining visual outcome, length of hospital stay, intra op carotid injury, inpatients death, risk of post-operative CSF rhinorrhea and diabetes insipidus.

KEYWORDS : Pituitary adenoma, Endoscopic transnasal, Charlson's comorbidity score, Frailty index, CSF rhinorrhea, Diabetes Insipidus.

1 INTRODUCTION

The management of neurosurgical conditions in the elderly and the frail brings with it, its own unique challenges. The process of ageing induces changes in the physiology of organ systems, tissue healing and immune response, which in turn determines recovery following surgical procedures. In addition to physiological changes of aging, a greater incidence of co-morbidities like coronary artery disease, poorly controlled hypertension etc is usually present in the elderly (>60 years).[1] Olshansky has defined 60 years of age as a cut-off for defining elderly, with patients over 80 years of age falling within the very elderly category. Current Indian population consists of 13% adults over the age of 60 years[2], which in turn translates to a large pool of ageing patients who require medical treatment for variety of diseases.

The pituitary, though small and weighs only 0.6 grams, has an important role to play, in the hormonal equilibrium that maintains homeostasis of the body, and its function therefore affects every major organ system in the body. Tumours arising from the gland can produce hormones, which are called functioning pituitary adenomas and the tumours that do not produce hormone are called non-functioning pituitary adenomas. These tumours may therefore pose both a problem of local mass effect, pituitary deficiency and systemic hormonal hyperactivity, which make these tumours difficult to understand and necessitates a meticulous presurgical work-up, including endocrinologists, radiologists, ophthalmologists and neurosurgeons, and warrants

regular post-surgical follow up with endocrinologists for optimal management of hormonal status.

Pituitary adenoma in adults mostly present as non-functioning adenoma and functional adenoma comprises mostly GH secreting adenoma.[3] Non-functioning pituitary adenomas are benign tumors that usually present with signs of mass effect over the optic chiasm. The patient may also develop clinical features of hypopituitarism. However, in the elderly, because of many common symptoms that occur in a pituitary macroadenoma, like worsening of eyesight, decreased exercise tolerance, loss of libido, amenorrhea etc[4], can also be attributed to physiological changes of aging, they are neglected and therefore there is delay in diagnosis.[5]

The endoscopic transnasal approach is widely accepted as an optimal treatment modality for PA. A review of literature shows that surgery in elderly patients carries a greater risk of post operative morbidity and mortality. Grossman et al showed that the overall surgical morbidity and mortality were greater for elderly patients who underwent surgery for PA. Higher number of complications were reported in elderly patient (>60 years) including CSF rhinorrhoea, vascular complication including pseudo aneurysm formation and hypopituitarism.[6]

Large series reporting on post-surgical outcomes consists of a both younger and older individuals, with younger individuals present in larger numbers. Due to these reasons, the complication profile as well as hormonal and visual outcome do not accurately depict the results that may be seen in more elderly patients. The burden of morbidity in terms of post operative CSF rhinorrhea, visual deterioration following surgery, incidence of hypopituitarism etc. have been reported in greater frequency

among the elderly. The incidence of medical complications like myocardial infarction and pulmonary embolism following transnasal endoscopic surgery is also reported with greater frequency in the elderly. However, age alone may not be the only factor that contributes to the outcome following surgery. The fallacy of using the age criteria alone as a means for shortlisting surgical candidates is that it overlooks the physiological status of the individual. Hence, it is also necessary any study evaluating post-surgical outcomes in the elderly should also consider the burden of associated co-morbidities that each individual carries. Various scales have been used to determine the co-relation between co-morbidities and surgical outcome, for instance Charlson comorbidity score is a scoring system that is used in predicting inpatient mortality or complicated postoperative recovery without considering the pathology and the anatomical location of the lesion .[7]

Hence by choosing a single pathological condition and a single surgical procedure, we attempt to further delineate preoperative clinical parameters that influence the visual, hormonal, and surgical outcome following surgery. In the elderly population, these prognostic factors may have a significant impact on the quantifying the risks and benefits of surgical management as these patients often present with a greater number of medical comorbidities and less physiological reserve, predisposing them to an increased rate of surgical complications and delay in recovery, It will also help the neurosurgeon to identify the patients who are most likely to benefit from surgery and the group which may be managed conservatively.

We also attempt to identify factors that might determine the outcome in these patients. We have compared the outcome in the cohort of elderly patients (age>60)

with a cohort of patients aged between 45-60 years. Clinical scores used for surgical risk stratification (ASA) and comorbidity scores (Charlson comorbidity score and frailty index) were used to delineate if the physiological status before surgery influences the outcome following treatment. This will be done to identify factors unique to the population of elderly patients.

To the best of our knowledge, no previous Indian study looked into the outcome and complication of endoscopic trans nasal pituitary adenoma surgery in elder population.

Charlson Comorbidity Index

The Charlson Comorbidity Index estimates survival in patients with multiple comorbidities. It consists of 19 items that are related to various health conditions that are associated with mortality. The Charlson's index can predict short and long-term outcomes**,** including function, length of hospitalization, and mortality rates. Among these 19 items, each item can be scored from **0 to 6 points**, and each has a different weight (which is based on the strength of the item's association with 1-year mortality, as presented in the paper by Charles et al.)[7]. Therefore some variables can score only 1 point at most (e.g. history of the myocardial infarction), while others can score as many as 6 points (e.g. metastatic tumor). **(Figure 1)**

- If the comorbidity is **not present**, patients score **0 points** for that comorbidity.
- Patients who are **50 years old or more** should get additional points as follows:
    - 50-59 years old - additional 1 point
    - 60-69 years old - additional 2 points

- 70-79 years old - additional 3 points; and
- 80 years old or more - additional 4 points.

The maximum Charlson's Comorbidity Index score (adjusted for age) is **37 points**

Figure 1: Charlson Comorbidity Index

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or several renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumour without metastases (exclude if >5 years from diagnosis)
	Leukaemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AIDS (not just HIV-positive)

Abbreviations: AIDS = acquired immunodeficiency syndrome; CVA = cerebrovascular accident; ECG = electrocardiogram; HIV = human immunodeficiency virus; TIA = transient ischaemic attack

* For each decade >40 years of age, a score of 1 is added to the above score

Frailty index

Frailty is defined as a process of progressive multisystem decline which leads onto diminished physiological reserve and poor capacity to respond to physiological stress.[8] Frailty has a high prognostic value in primary care practice as it can be incorporated as a diagnostic tool for many clinical decisions and discussions. However, there are limited data in quantifying frailty and its association with postoperative complications, which may contribute to the high morbidity and mortality observed in the Indian population.

The **frailty index** (**FI**) is used to measure the health status of older individuals, it serves as a proxy measure of aging and vulnerability to poor outcomes. FI is defined as the proportion of deficits present in an individual out of the total number of age-related health variables considered. A frailty index can be created in most secondary data sources related to health by utilizing health deficits that are routinely collected in health assessments. These deficits include diseases, signs, symptoms, laboratory abnormalities, cognitive impairments, and disabilities in activities of daily living.[9]

Frailty Index (FI) = (number of health deficits present) ÷ (number of health deficits measured)

We have taken below mentioned 20 points parameters to calculate frailty index (figure:2)

Figure 2: Modified frailty Index parameters

MFI clinical deficits	(Total=20)
1. Cerebrovascular accident or transient ischemic attack	1
2. Impaired cognition (dementia, Alzheimer's dementia)	1
3. History of recurrent falls	1
4. Diabetes mellitus (except diet-controlled)	1
5. History of syncope or blackouts	1
6a. Ambulatory with no assistive devices or	0
6b. Ambulatory with walker or cane or	1
6c. Nonambulatory or use of scooter/wheelchair	2
7. Psychiatric disorder (posttraumatic stress syndrome, bipolar disease, paranoia, schizophrenia)	1
8. Thyroid disease	1
9. History of seizures	1
10. Congestive heart failure	1
11. Depression	1
12. History of malignancy	1
13. Decubitus ulcers	1
14. Cardiac disease (coronary artery disease, arrhythmia, mitral valve prolapse, aortic stenosis)	1
15. Urinary incontinence	1
16. Parkinson's disease	1
17. Renal disease (acute or chronic)	1
18. Respiratory problems (COPD, emphysema, OSA, chronic bronchitis)	1
19. History of myocardial infarction	1

COPD=Chronic obstructive pulmonary disease, OSA=Obstructive sleep apnea, MFI=Modified frailty index

Previous studies have demonstrated an association between frailty and a number of outcomes for neurosurgical patients [10-14].

Results from our current study is consistent with these results and it's an accessible tool to increase the clinical usability of frailty as a predictive marker.

ASA Physical Status Classification System

The ASA Physical Status Classification System has been in use for over 60 years. The purpose of the system is to assess and communicate a patient's pre-anaesthesia medical co-morbidities. The classification system alone does not predict the perioperative risks, but used with other factors (eg, type of surgery, frailty, level of deconditioning),

it can be helpful in predicting perioperative risks.[15] The different grades of ASA has been depicted in the table below.

Figure 3: ASA physical status (PS) classification and definition *(Taken from https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system)*

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations. One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/ thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Four retrospective studies on elderly patients with intracranial meningiomas reported postoperative mortality as the primary outcome measure. In 3 of these studies, the association of the higher ASA physical status classification scores and mortality was significant.[16,17,18,19]

A retrospective study on 96 elderly intracranial meningioma patients concluded that a preoperative ASA physical status classification score of III or IV predicts poor outcome.[20]

Two studies have demonstrated the higher preoperative ASA physical status classification scores were associated with an increased incidence of postoperative meningitis and infection rates.[21, 22]

Our study adds to the knowledge about anticipated complication and outcome according to age group, which helps in the better planning and management of patients based on age and associated comorbidities and helps in pre operative counselling and explaining the possible outcome to patients and their relatives.

AIMS OF THE STUDY

1. To determine the factors responsible for post-operative visual, hormonal and surgical outcomes in elderly patients (>60 years) following endoscopic transnasal approach for pituitary adenoma (PA).
2. Comparison of surgical outcomes in patients aged > 60 years to a younger cohort of patients (age 45-60 years) and to evaluate the factors that determine the risk of developing morbidity and mortality in the elderly population.

2 LITERATURE REVIEW

Tumors of the pituitary gland and sellar region constitute 10 to 15% of intracranial neoplasms[23]. Incidence of pituitary tumors increases with age with 9% of the tumors occurring in population under 20 years of age and 30% of the tumors occurring in the age group between 50 and 60 [24,25]. In 2017, the World Health Organization (WHO) classified tumors of the pituitary gland into the following types: pituitary adenoma, pituitary carcinoma, pituitary blastoma, tumors of the posterior pituitary, Neuronal and para-neuronal tumors, craniopharyngioma, mesenchymal tumors, germ cell tumors, secondary tumors and haematological tumors[26]. Pituitary tumors are classified as functioning and non-functioning based on hormone secretion. Non-functioning pituitary adenomas (NFPAs) are benign neoplasms that originate from the adenohypophyseal cells and are not associated with clinical evidence of hormonal hypersecretion[27]. The functioning pituitary adenomas causes increased secretion of one or multiple hormones of the anterior pituitary depending on the cell type that causes the tumour. Pituitary adenoma can be classified as microadenoma, macroadenoma, and giant tumors based on size. Microadenoma is a tumour less than 10 mm, while macroadenoma describes a tumour larger than 10mm. Giant pituitary tumors are bigger than 40 mm[28]. Surgery forms the mainstay in the management of all these pituitary adenomas.

Classification of pituitary adenomas

A. Pathology

The pituitary is composed of two lobules, an anterior adenohypophyseal portion and a posterior neurohypophyseal portion. The two parts are morphologically, embryologically and functionally different. Pituitary adenomas arise from the anterior lobule, whereas tumours from the posterior lobe are very rare. The most common tumours encountered in the posterior lobe are metastases from malignant tumours elsewhere in the body [29].

Pituitary adenomas have traditionally been classified according to their light microscope appearance:

Chromophobe – the most common tumours, they were originally thought to be non-secretory, but it was later shown that they may produce prolactin (PRL), growth hormone (GH) or thyroid-stimulating hormone (TSH).

Acidophil – produce prolactin, TSH or, usually, GH

Basophil – produce gonadotropins (follicle-stimulating hormone (FSH) or luteinizing hormone (LH)) or adrenocorticotrophic hormone (ACTH)

The modern pathologic classification is based on immunohistochemistry, which permits conclusive identification of the various cell types in the adenoma. The standard immunohistochemical battery includes the use of antibodies to GH, PRL, ACTH, TSH, FSH, LH and the alpha-subunit of the glycoprotein hormones [30].

Most pituitary adenomas arise sporadically or, rarely, as part of hereditary genetic syndromes. Molecular analysis of familial pituitary adenomas has provided significant insight into pituitary tumorigenesis. Some specific genes have been identified that predispose to pituitary neoplasia, but these are rarely involved in the pathogenesis of sporadic tumours. One known genetic disorder that predisposes individuals to pituitary adenomas is multiple endocrine neoplasia type-1. This is a rare, autosomal-dominant disorder that gives rise to tumours in the parathyroid, pancreas and pituitary. It accounts for approximately 3% of all pituitary tumours [31]. Lately there has been special focus on pituitary adenoma predisposition caused by germline mutations in the AIP gene, first described by a Finish group in 2006 [32]. This condition has later been known as Familial Isolated Pituitary Adenomas (FIPA) and FIPA families account for around 2% of pituitary adenomas [33]. The number of other identified genes is increasing. The possible resulting mechanisms of action involve abnormalities in signal transduction pathways, cell cycle regulators, growth factors and chromosome stability [34].

B. Clinical classification

Pituitary adenomas can be classified based on their secretory products. The most common tumours, constituting approximately 65% of all tumours, are the endocrine active tumours that produce one or two hormones that can be measured in the serum and causes distinct clinical syndromes.

Prolactin – amenorrhea, galactorrhoea, infertility, impotence, etc.

Growth Hormone – acromegaly or gigantism

Thyroid Stimulating Hormone - secondary hyperthyroidism

Adrenocorticotropic Hormone – Cushing's disease or Nelson's syndrome

The other group of tumours are the endocrine inactive tumours, consisting of 5 subgroups

Null – cell adenoma
Oncocytoma
Gonadotropin – secreting adenoma
Silent corticotrophin – secreting adenoma

Glycoprotein – secreting adenoma

C. Classification by size

Pituitary adenomas can also be classified based on their size

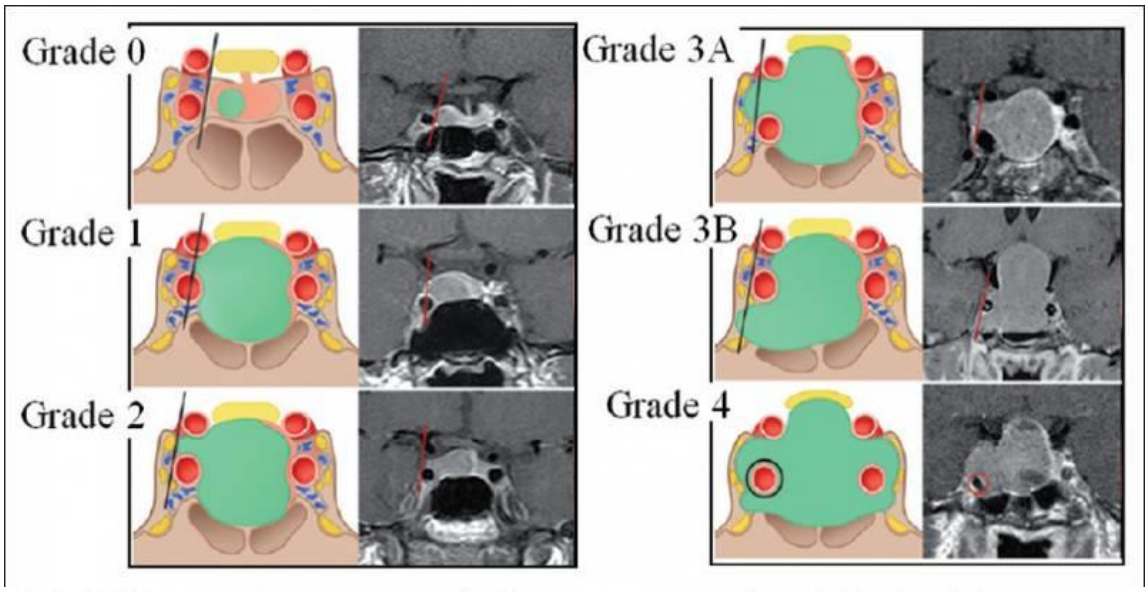
Microadenoma – less than 10 mm in diameter

Macroadenoma – more than 10 mm in diameter

D. Classification based on lateral growth

A simple and surgical relevant classification of pituitary adenomas is by their extent of lateral growth. There are many variants proposed for this classification, but the most used today is the Knosp classification [35] illustrated in figure 4.

Fig 4: KNOSP Grading



Clinical symptoms of pituitary adenomas

Pituitary adenomas are usually divided into secreting and non-secreting tumours. Non-secreting tumours do not present until they are large enough to cause neurologic symptoms due to their mass effect, whereas secretory tumours present earlier due to the physiologic symptoms caused by the excess hormones they secrete. The symptoms and signs of pituitary adenomas can be divided into three main groups:

- endocrine symptoms
- mass effect symptoms
- pituitary apoplexy

Endocrine symptoms

Approximately 65% of pituitary adenomas secrete an active hormone (48% prolactin, 10% growth hormone, 6% ACTH and 1% TSH) [36].

Prolactin hypersecretion causes amenorrhoea-galactorrhoea syndrome, with infertility in females and impotence in males. It can be caused either by a prolactinoma, a neoplasia of pituitary lactotrophs or by the so called "stalk- effect" – a non-secreting tumour that puts pressure on the pituitary stalk and thereby reduces the hypothalamic inhibitory control over prolactin secretion.

Growth hormone over-secretion causes acromegaly in adults and gigantism in children and adolescence before closure of the growth plate.

ACTH hypersecretion causes an endogenous hypercortisolism, also termed Cushing's disease. In patients who have undergone adrenalectomy, ACTH over-secretion might cause Nelson syndrome.

TSH hypersecretion is clinically detectable as a secondary or central hyperthyroidism.

LH and/or FSH hypersecretion will usually not produce a clinical syndrome.

Endocrine symptoms may also present as pituitary deficiency; this effect may be caused by the compression of the normal pituitary by a large non-secreting tumour. There seems to be a fixed order of sensitivity to compression of the hormone-producing cells, with growth hormone being lost first, followed by gonadotropins,

TSH and ACTH. Selective reduction of a single pituitary hormone is very rare in adenomas and points to some other cause, such as autoimmune hypophysitis, hypothalamic glioma or craniopharyngioma.

Mass effect

Growing pituitary adenomas may be detected by compression on their neighbouring structures

- dura and skull base – may give rise to headache
- optic chiasm – causes bitemporal hemianopsia and subsequent

  reduced visual acuity

- third ventricle – may cause obstructive hydrocephalus
- cavernous sinus – compression of the contents of the cavernous sinus (cranial nerves III, IV, V1, V2 and VI and carotid artery) may give rise to ptosis, facial pain and diplopia

Pituitary apoplexy

Pituitary apoplexy is a sudden intrasellar expansion due to haemorrhage and/or infarction within a pituitary tumour and adjacent pituitary gland [37]. Seldom, a haemorrhage may occur in a normal pituitary gland. Symptoms of pituitary apoplexy include the following: sudden onset of headache, visual disturbances and loss of consciousness. The true incidence of apoplexy in an adenoma is difficult to

assess; in one much-cited series, 3% of patients with macroadenomas had an episode of apoplexy [38].

Diagnosis of pituitary adenomas

History and Physical examination

General clinical and neurological examination directed at finding signs and symptoms of

- Endocrine dysfunction
- Visual field deficits
- Cranial nerve palsies

Endocrinologic evaluation

A thorough endocrine evaluation is necessary to verify type of tumour, to determine whether there is a need for hormonal replacement and to establish a hormonal baseline for endocrine follow-up after treatment. All axes need to be checked.

- Adrenal axis screening
    - 8 AM cortisol
    - 24-hour urinary free cortisol if hypercortisol is suspected
- Prolactin levels
    - moderately elevated may indicated prolactinoma or a " stalk effect"

- significant elevation is indicative of a prolactinoma

- Thyroid axis
  - freeT4andTSH
- Growth hormone axis
  - IGF-1
  - A single random GH level is not reliable
- Gonadal axis
  - Serum gonadotropins, FSH and LH o Sexsteroids
    - oestradiol in women
    - testosterone in men
- - Neurohypophysis
    - P-Na and P-osmolality
    - U-Na and U-osmolality
    - check the ability to concentrate urine with water deprivation.

Visual evaluation

A formal preoperative visual evaluation is mandatory in the presurgical work-up and should include both an evaluation of visual fields and visual acuity. Goldmann perimetry is the most widely used test for visual fields [39].

A variety of pathologies can cause particular type of visual field defect indicating the site of the neurological damage. A lesion in the optic nerve can cause complete visual field loss in the ipsilateral eye called as monocular visual loss. Lesion in the middle portion of the optic chiasm most commonly caused by pituitary tumours affects the fibres crossing from the nasal retina of each eye, leaving the uncrossed fibres from the temporal retina intact. This results in loss of vision in the temporal visual field of each eye and is known as bitemporal hemianopia. Homonymous hemianopia is caused by a lesion in the optic radiation on the contralateral side of the anopia. Homonymous hemianopia with macular sparing is caused by a posterior cerebral artery (PCA) stroke. The macula is spared because of its dual blood supply from both the middle cerebral artery (MCA) and the posterior cerebral artery. Any lesion in the temporal lobe causes superior quadrantanopia. A lesion in the parietal lobe causes inferior quadrantanopia. Lesions of macula causes defects in the central vision leading to central scotoma.

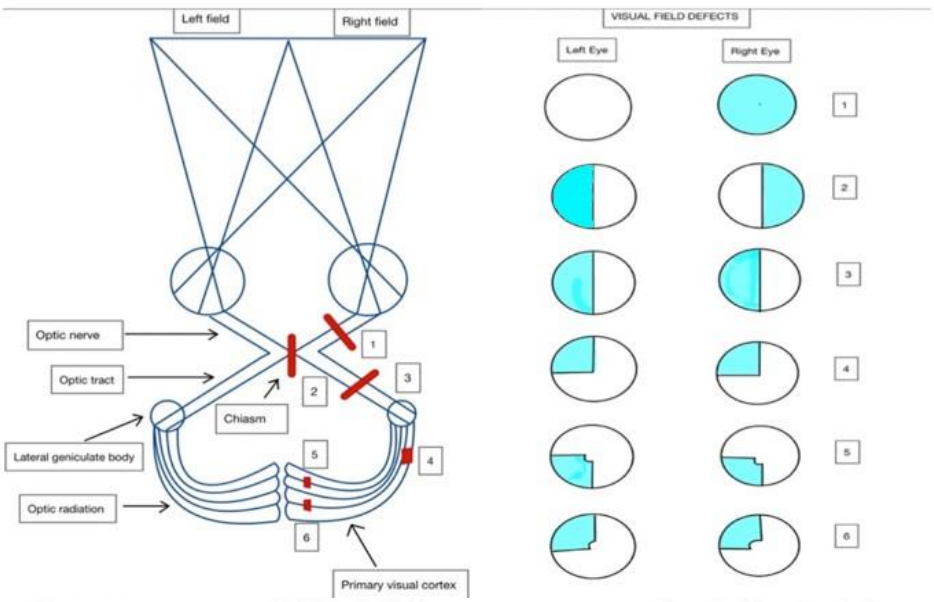


Fig 5: shows the description of Lesions at various levels in the visual pathway and the type of visual field defect

Neuroradiologic evaluation

CT SCAN

A cerebral CT- scan may be indicated for surgical planning as it shows the shape of the sphenoid sinus, the presence of septa in the sinus, and the presence of a septal deviation in the nose and co-registration with bony landmarks. Additionally, evaluation for anatomic variants such as under-pneumatization of the sphenoid sinus or dehiscence of the bony roof overlying the internal carotid arteries is better using CT than MRI. CT

angiography can be useful in evaluating for cavernous sinus invasion, as this impacts preoperative planning.

The differences in attenuation of bone and calcified products to liquids and soft tissues make CT ideal for evaluating calcification or ossification within suprasellar lesions. This property is useful in distinguishing calcifications within a craniopharyngioma from hemorrhage within a pituitary adenoma since both may appear similar on magnetic resonance imaging (MRI).

MRI SCAN

A MRI of the brain and sellar region with multiplanar thin sections is the most important preoperative neuroradiologic evaluation. This imaging protocol provides axial, coronal, and sagittal sections of the sellar contents. Generally, the relationship between the lesion and the optic chiasm and visual pathways is easily recognized. Pregadolinium and postgadolinium images are recommended to ensure that primarily isointense lesions do not escape detection. This MRI will often show the adenomas relation to the normal pituitary gland. Most microadenomas have a low signal on T1-weighted images and high signal on T2- weighted images. Contrast enhancement is time dependent. Initially the normal pituitary will enhance to the greatest degree, but after approximately 30 minutes, the tumour and normal pituitary will enhance to similar degrees. Dynamic MRI scans have been attempted to look for tumours that are not observed on standard scans [40]. Deviation

of the pituitary stalk may also indicate on which side an isointense microadenoma is located.

A specialized form of neuroradiologic evaluation is Inferior Petrosal Sinus Sampling (IPSS), performed by an interventional neuroradiologist and used in the work-up for endogenous Cushing's syndrome. In this evaluation, microcatheters are advanced to the inferior petrous sinus and used to measure ACTH levels on both sides of the pituitary. IPSS is used in cases where a pituitary adenoma cannot be visualized on MRI. ACTH levels are measured before and after intravenous corticotropin releasing hormone (CRH) is given, and a central- to-peripheral ratio of more than two before CRH administration, or more than three after, is usually interpreted as positive for Cushing's disease [41].

Treatment of pituitary adenomas

The therapeutic toolbox includes careful observation, medical treatment, surgical resection, conventional radiation therapy and radiosurgery. In each patient, the risk and benefit of each therapy must be carefully assessed, and an individual treatment plan should be provided.

The goals of treatment are

- to reverse endocrinopathy and restore normal pituitary function to eliminate the mass effect of the tumour
- to reduce the likelihood of tumour recurrence
- to obtain a definite histologic diagnosis

Observation

Careful observation with repeated MRI-scans, visual evaluation and endocrine

evaluation may be a good treatment option for small non-functioning tumours without visual impairment and where there is no indication for surgical treatment. Studies have shown that only approximately 10% of non-functioning microadenomas and 24% of non-functioning macroadenomas will grow and require treatment [42].

Non-surgical treatment

Medical treatment

Medical therapy is first-line treatment for prolactinomas, and there can be a dramatic shrinkage of the tumour during treatment with dopamine agonists within days to weeks [43]. The most commonly used dopamine agonists are as follows:

- - bromocriptine, a dopamine agonist
- - cabergoline, a selective D_2 dopamine agonist
- - pergolide, a long-acting dopamine agonist

For growth hormone secreting tumours, surgery is still the primary treatment modality. However, medical treatment may be used as pre-treatment before surgery[44] for those who are not cured by surgery and for those with contraindications for surgery [45]. There are different medical options, and a combination of medication gives the best result in some cases

- - bromocriptine, a dopamine agonist
- - octreotide/ lanreotide/ pasireotide, somatostatin analogue
- - pegvisomant, GH receptor antagonist

Surgery is the primary treatment modality for patients with Cushing's disease. There are some medical treatment options that can be used prior to surgery to control the symptoms of Cushing's disease, including diabetes mellitus, hypertension, psychiatric disturbances etc.[46]. There are different options for medical treatment, some of the most commonly used are as follows:

- - ketoconazole, an antifungal agent that blocks adrenal steroid synthesis
- - aminoglutethimide, inhibits an enzyme in the synthesis of steroids from cholesterol
- - metyrapone, an enzyme inhibitor, inhibits cortisol synthesis
- - mitotane, inhibits several steps in glucocorticoid synthesis
- - cyproheptadine, a serotonin receptor antagonist, is effective in a small

percentage of patients.

Transsphenoidal surgery is the first-line treatment for TSH secreting tumours , but octreotide may help in cases where the patient is not cured [47].

Radiation therapy

Radiation therapy, either given as conventional fractionated radiotherapy or as radiosurgery, is no longer routinely used as primary treatment of pituitary adenomas, but it may have a role as postoperative treatment in selected patients [48,49]. Radiation therapy should be reserved for those cases in which it is not possible to remove the recurrent tumour and growth is documented. Prolactinomas seem to have a very poor response to radiation therapy. Growth hormone-secreting

tumours may have the best response, although the response is delayed for many years[50]. The side effects of radiation therapy may be hypopituitarism with progression to panhypopituitarism over a period of years, optic nerve and chiasma injury, memory disturbances and cranial nerve palsies[51].

Surgical treatment

Indication

A clear indication for surgery is progressive mass effect from a macroadenoma, causing visual impairment. The exception is prolactinomas, in which immediate and effective shrinkage can be achieved with medical therapy. The most urgent cases are pituitary apoplexies, for which abrupt vision loss, neurologic deterioration and collapse from acute adrenal insufficiency necessitates urgent glucocorticoid replacement and surgical decompression.

The secretory adenomas where surgery is the first-line treatment include Cushing's disease[52], secondary hyperthyroidism and growth hormone hypersecretion. In the treatment of acromegaly and gigantism, one often uses a combination of surgical and non-surgical therapies.

Failure of prior therapy is also an indication for surgery. Patients who are initially treated with medical therapy for acromegaly or prolactinomas that have an insufficient response to medication or intolerable medication side effects are clear candidates for surgical therapy. A surgical resection may be curative or reduce the tumour burden, leading to a

more favourable pharmacologic response. Patients who are initially treated with radiotherapy may also have a relapse after a number of years and require surgical therapy.

A relative indication for surgery is to obtain a definite histological diagnosis of a sellar tumour mass, e.g., in the case of a radiologically verified tumour in a patient with known history of a metastatic tumour.

Contraindications for surgery

Surgery for pituitary adenomas are in most cases minimally invasive microsurgical or endoscopic transsphenoidal surgeries, and there are few contraindications. Absolute contraindications for transsphenoidal surgery would be as follows:

- sinusitis or active systemic infection
- "kissing carotids", in which the horizontal distance between the two
- carotid arteries is less than 10 mm and there is insufficient space to perform surgery
- very poor general medical condition of the patient [53]

Relative contraindications for surgery would be

- severe cardiovascular compromise
- chronologic age of the patient
- severe endocrine disturbances
- florid Cushing's disease
- grave acromegaly

- serious secondary hyperthyroidism

It will often be possible to improve the consequences of these endocrine disturbances with medication before surgery and thereby reduce the increased anaesthetic risk

Choice of surgical method

Approximately 95% of the pituitary adenomas can be resected through a transsphenoidal approach, either with a microscopic or an endoscopic technique. Other cases require a transcranial approach.

Factors that favour a transcranial approach are as follows:

- - significant suprasellar and especially anterior or posterior extension of the tumour
- - an hour-glass shape of a tumour, with a small opening in the diaphragma sellae
- - if the tumour is suspected to be very firm in consistency, e.g., multiple previous surgeries
- - if one is in doubt about the nature of the tumour (e.g., suspecting a meningioma)

Transsphenoidal surgery

The transsphenoidal approach to the sella turcica is a minimally invasive, direct approach through the air sinus system of the anterior skull base. It has become the access route of

choice because it requires no brain retraction and provides direct visualization of the pituitary and adjacent structures.

The surgical technique has evolved over the years, with better illumination from modern microscopes and endoscopes, the use of endonasal rather than sublabial access to the sinus system, the use of better methods for reconstruction of the dura and sellar floor and the development of better micro-instruments for dissection and tumour removal.

Even though this is an excellent surgical route to reach sella turcica, it has its limitations. The long and narrow surgical corridor creates a very limited space in which to move the instruments and to actually perform the surgery; the long corridor makes lateral and suprasellar visibility limited; the important neighbouring structures, such as the optic chiasm and carotid arteries, necessitate great care during the dissection; and the lack of landmarks inside the tumour makes it difficult to be certain how much of the tumour has been removed.

The cure rate for hormone-producing macroadenomas is in the range of 30-60%. In non-functioning macroadenomas radical surgery is obtained in 40 – 60%. The percentage of patients needing reoperations is 5-30%, the risk of complications after reoperations is markedly increased, and the long-term mortality in patients with recurrent tumours is markedly increased[54]. All of these data indicate the need to strive for more radical surgery. The following strategies may contribute to more radical surgery.

- immediate postoperative MRI

- intraoperative MRI

- intraoperative ultrasound

- neuronavigation on preoperative MRI/CT

- endoscopic endonasal techniques - experienced surgeons

Surgical techniques

Microscopic transsphenoidal surgery

Before 2005/2006, the standard microsurgical endonasal transseptal approach was used. The right nostril was entered, an incision was made in the anterior portion of the septum, and a dissection of the mucosa from the septal cartilage and bone was performed. The anterior wall of the sphenoid sinus was opened bilaterally, and any septum in the sphenoid was removed as necessary. The floor of the sella was opened with a high-speed drill, and the tumour was removed

Endoscopic endonasal transsphenoidal surgery

Beginning in 2005, the endoscopic endonasal transsphenoidal approach was gradually introduced. One or both nostrils were entered, depending on the space available and the need for exposure during surgery. Standard Storz endoscopes (180/4 mm) with 0°, 30° and 45° angulations (attached to cameras) were used. In the later period of the study, the endoscopes were attached to high-definition (HD) cameras. Based on personal preference, some surgeons used a fixed endoscope support, whereas others did not. The middle turbinate was lateralized to improve access to the sphenoethmoidal recess and the sphenoid ostium, that was identified and enlarged to allow the passage of the endoscope

and surgical instruments. Septa in the sphenoid sinus were removed as necessary. Tumour resection was performed with standard surgical instruments, such as curettes, dissectors, suction and micro forceps, depending on tumour size and firmness. In tumours with parasellar extensions, an ultrasonic Doppler probe was used to localize the internal carotid arteries. As a result of the broader view that was possible with the endoscope, the opening of the sella was extended, which made the closure of the sella floor more challenging. Sella floor reconstruction was most often performed in a multilayer fashion with different autologous and artificial materials. A vascularized nasal septal flap was also used as needed.

Complications after surgery for pituitary adenoma

The minimally invasive nature, the lack of an external scar and lower morbidity and mortality compared with transcranial approaches make the transsphenoidal approach to the pituitary appealing both to the patient and to the surgeon[55]. Transsphenoidal surgeries for pituitary tumours are among the safest procedures in neurosurgery, and almost certainly the safest major intracranial procedure[56]. When developing and adopting new surgical techniques, it is necessary to know your previous success rates and complication rates to be able to judge whether the changes you made have positive or negative results.

It may be useful to divide complications after transsphenoidal surgery into three different categories:

-nasal complications

- endocrine complications

-surgical complications

Nasal complications include anosmia, chronic sinusitis and septum perforation. Endocrine complications include new anterior lobe deficits, diabetes insipidus and SIADH. Surgical complications include postoperative CSF-leakage, meningitis, neurological deterioration, vascular complications and surgical mortality.

Another way to divide complications is into mortality, major morbidity and lesser morbidity. In recent years, the complication rates in centres of excellence in pituitary surgery are a mortality of approximately 1%, major morbidity approximately 3% and lesser morbidity approximately 5%[57].

Results after surgery for pituitary adenomas

Non-functioning adenomas

The outcome regarding visual function after transsphenoidal surgery is usually excellent, and the quality of life is among the best in the field of neurosurgical tumours[58]. However, many patients will have tumour remnants after surgery[59], and tumour recurrence is not infrequent. Large and giant macroadenomas pose the greatest challenge to the pituitary surgeon and carry the highest risk of serious complications[60].

GH-secreting adenomas

The criteria for biochemical cure of acromegaly is not standardized and has changed over

the years, making outcome figures for acromegaly difficult to compare. However, it seems that transsphenoidal surgery results in remission in a large percentage of patients with microadenomas without invasive growth. GH-producing macroadenomas extend often laterally, with invasion into the cavernous sinus, making them difficult to cure with surgery. The development of medical treatment for acromegaly has been rapid and successful, therefore, there are now possibilities for adjuvant therapy that have few side effects and high effectiveness.

In the last consensus (2009) of the Acromegaly Consensus Group, optimal disease control is now defined as IGF-I level (determined by a reliable standardized assay) in the age-adjusted normal range and a GH level less than 1.0 μg/litre from a random GH measurement (using an ultrasensitive assay). In patients with acromegaly undergoing surgical management of GH-secreting tumours, oral glucose tolerance test (OGTT) can be used to assess the outcome. There is substantial evidence suggesting that nadir GH levels less than 0.4 μg/litre (with ultrasensitive assays) may define control in these circumstances. In the case of discrepant biochemical results, multiple GH sampling may be useful [61].

ACTH secreting adenomas

There are numerous methodologies for determining biochemical remission of Cushing's disease, however there is no international consensus on the criteria for remission. The most used criteria for remission are as follows: Clinical resolution of symptoms, normal 1 mg overnight dexamethasone suppression test (DST), normal urinary 24 h free cortisol and normal late-night salivary cortisol level[62]. A high proportion of patients will be cured with transsphenoidal surgery, with the best results in microadenomas visible on MRI

scans. As there are no effective medical treatments, the only other option to relieve the burden of Cushing's disease is to perform a bilateral adrenalectomy, a mutilating surgery that requires life-long glucocorticoid replacement, but that is occasionally necessary[63].

TSH-secreting adenomas

These adenomas are very rare, and there are few reports of results after surgery, but it appears that half of patients go into remission after transsphenoidal surgery, and one can achieve even better control with the addition of radiotherapy[64.]

Surgical Approaches to Pituitary Tumors And Their Relevance

The first surgical attempt to remove a pituitary tumour was described by the British general surgeon F. T. Paul, of Liverpool. Paul, on February 2nd 1893, at the suggestion of Sir Victor Horsley of London, performed a subtemporal decompression in an acromegalic patient suffering from headache, visual loss and facial pain [65]. The patient died 3 months later, and the autopsy revealed a tangerine-sized pituitary tumour. Horsley later operated upon 10 patients with pituitary tumours, using temporal and subfrontal approaches, and reported his results in 1906 [66]. The first attempt to approach a pituitary tumour through a transsphenoidal approach was made by Hermann Schloffer in 1907 in Vienna[67]. He used an extensive lateral rhinotomy to enter the nasal cavity, and then resected the septum and turbinates to obtain access to sella turcica.

In 1909, Harvey Cushing , who was an associate professor of surgery at Johns Hopkins University in Baltimore, described a refined variant of transsphenoidal surgery using a sublabial incision instead of a lateral rhinotomy[68]. Further development of the transsphenoidal approach was performed by Oskar Hirsch, a rhinologist from Vienna, who described the first endonasal approach in 1910 and later the submucosal transseptal route[69]. Cushing employed the transsphenoidal approach to the pituitary in more than 200 operations. However, by the late 1920s, he had abandoned the transsphenoidal approach in favour of the transcranial subfrontal route[70]. He could achieve a better decompression of the optic chiasm, a more complete evacuation of the sellar tumour, and a reduced risk of CSF leakage with the transcranial approach. Harvey Cushing had a tremendous impact on the practice of neurosurgery both in the

US and in Europe, and the transsphenoidal route to the pituitary was more or less abandoned for the next 40 to 50 years.

One surgeon who did not want to abandon the transsphenoidal route was Norman Dott. He learned this method as a fellow of Cushing and brought it with him to Edinburgh, where he had performed 80 consecutive operations without any deaths by 1956[71]. Gerard Guiot came to Edinburgh in 1956, learned the procedure from Dott and later performed more than 1000 transsphenoidal procedures in Paris. Guiot had many fellows who trained with him in Paris. Among them was Jules Hardy from Canada, who brought transsphenoidal surgery back to North America. Hardy developed a set of instruments specially designed for transsphenoidal surgery and introduced the operating microscope for pituitary surgery in 1967. Hardy and Guiot once again popularized transsphenoidal surgery in Europe and North America, and since the 1970s, transsphenoidal microneurosurgery has been an integral part of neurosurgery. The procedure was for a long time called CGH (Cushing-Guiot-Hardy) after the three pioneers.

Transsphenoidal surgery continued to develop during the 80s and 90s with the development of the direct endonasal approach and extended approaches allowing surgery in the vicinity of the sella[72]. Along the same line was the introduction of the endoscope into the sella, which was a spill-over from otorhinolaryngologists performing endoscopic sinus surgery, so called FESS surgery (functional endoscopic sinus surgery). Some centres developed the endoscopy assisted microsurgical transsphenoidal surgery[73], whereas others, such as Paolo Cappabianca in Naples, Hae Dong Jho in Pittsburgh and Giorgio Frank in Bologna, developed fully endoscopic

procedures[74,75,76]. Over the years, the fully endoscopic procedure has gained popularity, and there has been a rapid increase in the number of surgeons using this method.

> The endoscopic approach is minimally invasive with wider panoramic visualization, improved mobility of instruments and the ability to look around the corners with angled lens. Lack of bimanual dissection which was a concern for the surgeon in the initial times was overcome by bi-nostril approach now a days. The ability to identify key landmarks plays a vital role in endoscopic approaches for best outcomes.

The strive for better control over the amount of tumour tissue removed in the suprasellar and parasellar areas led to the development of intraoperative imaging during transsphenoidal surgery. Different intraoperative imaging techniques have been used, such as CT, ultrasound and MRI. Groups that have been instrumental in the development of intraoperative MRI are Peter Black's group in Boston, working with a 0.5-Tesla, "double donut" MRI, and Rudolph Fahlbusch's group in Erlangen, working with a 1.5-Tesla MRI-scanner[77,78]. Both groups showed that they could obtain high-quality images during transsphenoidal surgery and that they could visualize tumour remnants that could be removed later during the same surgery.

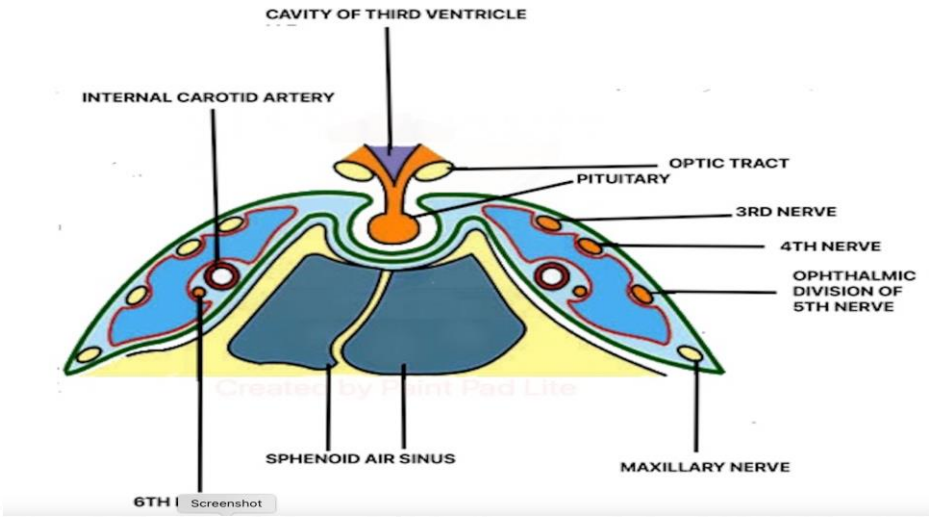


Fig 6: shows the anatomy of the pituitary gland-coronal section and its relationship with optic pathway

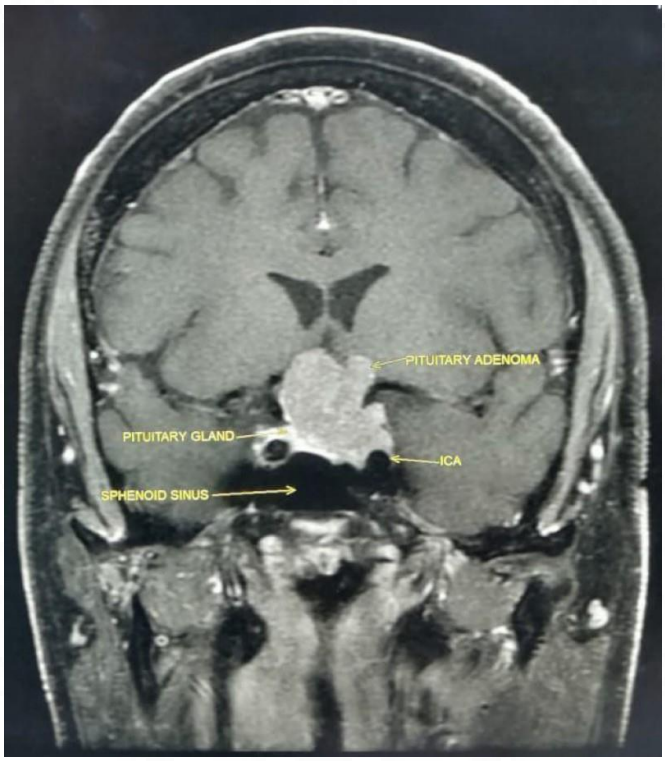


Fig 7: shows the MRI - coronal T1 post-contrast image of our patient showing a pituitary adenoma

Pituitary adenomas causing visual impairment are treated surgically to improve or halt further progression of vision loss as longer duration of the symptoms is associated with worse visual outcomes after surgery[79]. In these patients the improvement in visual field is rapid following surgery with most of the recovery occurring during the first three months of post-operative period[80]. Most of the studies showed acceptable visual outcome post-surgery but they are limited by the heterogenous groups of tumours and the evaluation of visual field and visual acuity at the time of presentation that was lacking. Fahlbusch, and Schott, et. al, showed that young age and short duration of symptoms were good prognostic factors for visual outcome[81]. Zevgaridis, et. al, showed age, symptom duration, preoperative visual function, and arachnoid membrane intactness as prognostic factors[82]. Margalit, et. al, highlighted the importance of optic nerve encasement, size of the tumour and preoperative visual function in prognostication[83]. However surgical manipulation is the most important factor that determines the postoperative visual function thereby monitoring of visual apparatus is an important priority.

The presence of pituitary adenoma in patients over 60 years old is a relatively common occurrence, with autopsy studies in the elderly and very elderly showing a prevalence of approximately 11– 14%[84]. The incidence of PA increases with age and elderly patients with pituitary adenomas often present with more advanced disease, including visual field defects, compared to their younger counterpart. Previous literature suggest that elderly patients with pituitary adenoma have highly variable range of outcome compare to their younger counterparts. Various studies have been conducted by including patients aged above 60 years. And have shown higher

complication rates in elderly population[3,5]. While Sheehan *et al.*[85] and Ferrante *et al.*[86] showed minimal post-operative complications without mortality, Pietila *et al*[87] reported 11% perioperative mortality, and 11% postoperative deterioration following surgery among patients aged from 80 to 86 underwent brain tumour surgery.

The safety and efficacy of neurosurgical intervention for elderly patients with pituitary adenomas, however, has thus far not been fully characterized, potentially complicating the surgical decision making process for such patients and their providers[88.] We report outcomes on 361 patients with pituitary adenoma underwent endoscopic transnasal pituitary adenoma resection between 2009 and 2021 at our institute and found to have the below mentioned results.

3 MATERIALS AND METHODS

AIM

1.To determine the factors responsible for post-operative visual, hormonal and surgical outcomes in elderly patients (>60 years) following endoscopic transnasal approach for pituitary adenoma (PA).

2.Comparison of surgical outcomes in patients aged > 60 years to a younger cohort of patients (age 45-60 years) and to evaluate the factors that determine the risk of developing morbidity and mortality in the elderly population.

DESIGN:

This is a retrospective study of all transnasal endoscopically operated patients with diagnosed pituitary adenoma above 45 years between year 2009 to 2021 (361 patients) in the Neurosurgery Department of Sree Chitra Tirunal Institute For Medical Sciences and Technology (SCTIMST). A formal clearance was obtained after.the evaluation of the study by the Institute Ethics Committee (IEC). (IEC NUMBER: IEC/1761, dated 26th November 2021)

DURATION OF THE STUDY: 1.5 years

FUNDING: There were neither external sources of funding nor conflicts of interest in thecurrent study

ETHICAL COMMITTEE CLEARANCE - The stud protocol was presented to the SCTIMST ethical committee and scrutinised at various angles regarding the aim of the study. The study was started after the formal clearance from the IEC.

SUBJECT /PARTICIPANT SELECTION:

Inclusion criteria:

All trans nasal endoscopically operated patients with diagnosed pituitary adenoma above 45 years

Exclusion criteria:

1. All younger patient with age below 45 years
2. Trans nasal endoscopically operated cases other than pituitary adenoma.
3. Whose regular follow up not available in our record system

INFORMED CONSENT – Consent was not required since it is retrospective observational study

METHODS

This was a retrospective study where of patients who were diagnosed with PA, were aged above 45 years and underwent endoscopic endonasal resection of pituitary adenoma between year 2009 to 2021. Demographic data of each patient including age, sex, comorbidities, pre and postoperative visual & hormonal status, tumor size, extent of resection, duration of hospital stay, surgical outcomes, complications and follow up at 3weeks, 3months and 1 year were collected from EMR available in institute. The data was analyzed using SPSS (IBM SPSS Statistics for Windows, Version 23.0.(Armonk, NY: IBM Corp).

No new investigations were carried out upon any patient

DATA ANALYSIS:

To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean, S.D (standard deviation) were used for continuous variables. The continuous variables were expressed as mean ± standard deviation. The mean differences were tested by a two-tailed t-test. Pearson's correlation was used to analyse the association between quantitative parameters. For categorical variables, the Chi-square test was used to determine if the observed results were in line with expected results. Plots and charts included box whisker plots, bar charts, and histograms for displaying the variation in the data set. For the multivariate analysis for repeated measures, analysis of variance (ANOVA) was used with Bonferroni correction to control the type I error on multiple comparison. In both the above statistical tools the probability value $p<0.05$ was considered significant.

4 RESULTS

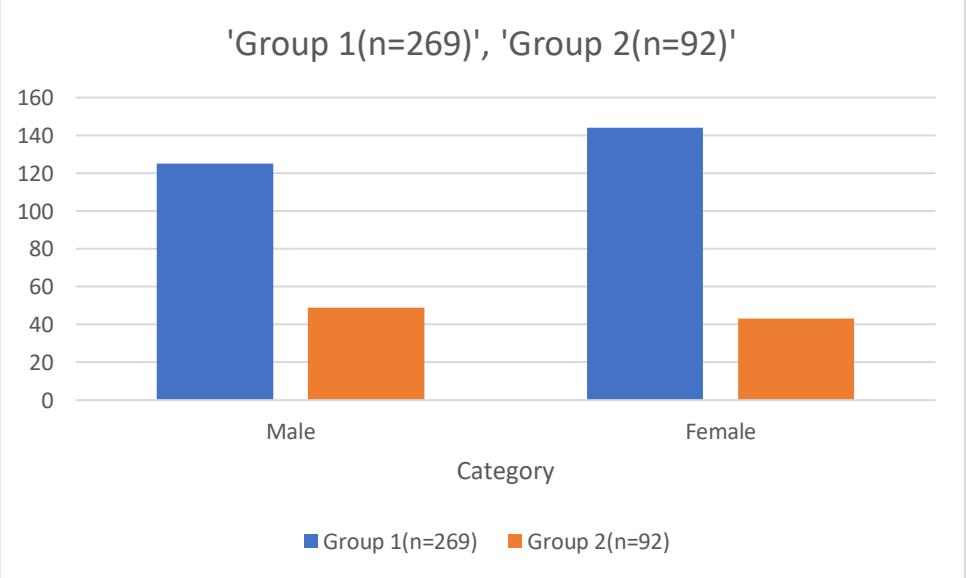
Demography

A total of 361 patients above the age of 45 years were included in the study. These patients were divided into two groups. Group 1 comprising of patients between 45-60 years included 269 (females-144, males-125) patients, and the group 2 comprising of patients aged > 60 years included 92 (females- 43, males- 49) patients.

Table 1: Age and sex category

		Age Category		
		Group 1 45-60yrs (n=269)	Group 2 >60years (n=92)	Total
Sex	Male	125	49	174
	Female	144	43	187
Total		269	92	361

Graph 1: Bar diagram showing age and sex distribution



Associated comorbidities

The distribution of patients according to ASA grade in group 1 was, ASA I - 22.3%, ASA II - 55.01%, ASA III - 21.9% and ASA IV - 0.7% , among this majority patients were ASA I and ASA II (208/269, 77.3%). The distribution of patients according to ASA in group 2 was, ASA I - 4.3%, ASA II - 59.8 %, ASA III - 32.6 % and ASA IV - 3.3%, among this majority patients were ASA 2 and ASA 3 (85/92, 92.4%).

The mean Charlson's score for group 1 was 3.071 and for group 2 was 4.800 **(p<0.001).**

The mean Frailty index for group 1 was 0.0666 and for group 2 was 0.1109 **(p<0.001).**

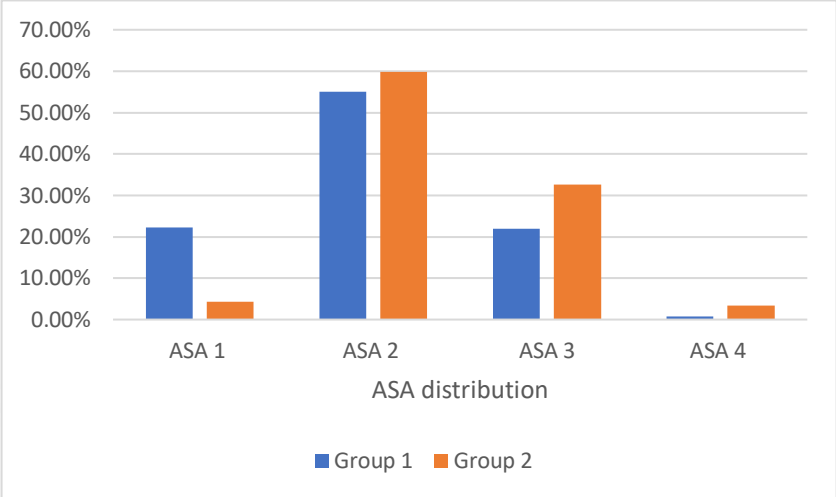
The Pearson Chi-square value of the comparison was 19.051 and **p<0.001**.

The preoperative Charlson's score showed strong correlation with the ASA score **(p<0.001)** and Frailty index **(p<0.001)**

Table 2: Comparison of associated comorbidities in the two groups

comorbidity scores	Category	Group 1(n=269)		Group 2(n=92)		p-Value
		n	%	n	%	
ASA Grade	ASA Grade I	60	22.3%	4	4.3%	**<0.001***
	ASA Grade II	148	55.0%	55	59.8%	
	ASA Grade III	59	21.9%	30	32.6%	
	ASA Grade IV	2	0.7%	3	3.3%	
Charlson's comorbidity index(CCI) score	Mean CCI score	3.074	NA	4.870	NA	**<0.001***
Frailty index	Mean frailty index	0.0666	NA	0.1109	NA	**<0.001***

Graph 2: Bar diagram showing distribution of ASA grades in the two groups



Preoperative presentation:

Pressure related symptoms was seen in 82.90% patients in group 1 and 86.96% patients in group 2 (p= 0.360).

Visual disturbances at presentation was seen in 78.81%(212/269) patients in group 1 and 84.8% (78/92) patients in group 2 (p=0.213). Visual acuity disturbances were present in 83.3% group 1 patients and 92.4% group 2 patients **(p=0.032).** Visual field deficits were seen in 89.1% of patients in group 2 as compared to 78.8% of group 1 patients **(p=0.028).** Visual field defects were seen in 89.1% of group 2 patients as opposed to 78.8% of group 1 patients **(p= 0.028).** The higher incidence of preoperative visual field defects were seen in patients with a higher Charlson's score of 5-6 (92.6%) and > 6 (92.9%) **(p=0.002).**

Headache was noted in 55.39% patients in group 1 and 50.00% patients in group 2 (p= 0.371).

Menstrual complaints was noted in 8.92% patients in group 1 and 0 %patients in group 2, as these patients were above 60 years **(p= 0.003).**

Apoplexy was noted in 6.31% patients in group 1 and 7.61% patients in group 2(p=0.668).

Seizures was noted in 3 (1.11%) patients in group 1 and none in group 2 (p=0.668).

Loss of consciousness was seen in 2 (0.74%) patients in group 1 and 1 (1.09%) patient in group 2 (p=0.754).

Cranial nerve deficits were seen in 8 (2.97%) patients in group 1 and 4 (4.35%) in group 2 (p= 0.526).

Limb weakness/hemiparesis noted in 6 (2.22%) patients in group 1 and 1 (1.09%) in group 2 (p= 0.492). The incidence of hemiparesis and cranial nerve palsies (4.7%, p=0.027) at presentation mainly noted in patients with a higher Charlson's score.

Extraocular muscle Palsy were seen in 12 (4.46%) patients in group 1 and 6 (6.52%) in group 2 (p= 0.433).

Cardiovascular complaints like palpitation and anxiety were seen in 61(22.68%) patients in group 1 and 31 (33.70%) in group 2 (**p= 0.031**).

Features of Hypopituitarism seen in 92(34.20%) patients in group 1 and 15 (16.30%) in group 2 (**p= 0.001**).

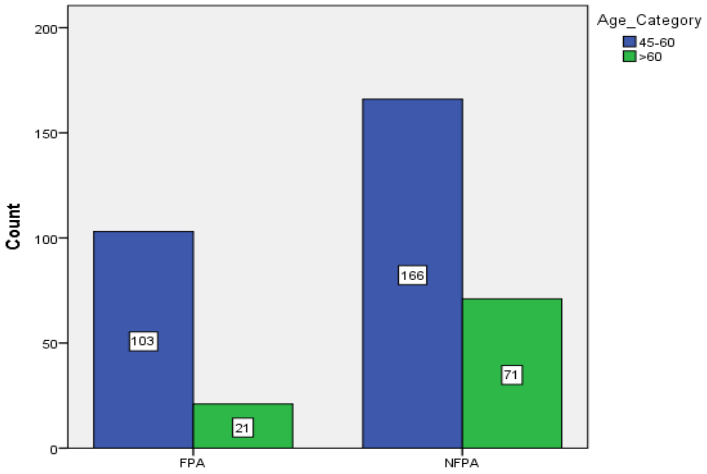
Loss of secondary sexual characteristics seen in 4 (1.49%) patients in group 1 and 1 (1.09%) in group 2 (p= 0.777).

Mean duration of symptoms were of 20.05 months in group 1 and 16.50 in group 2 (p= 0.298)

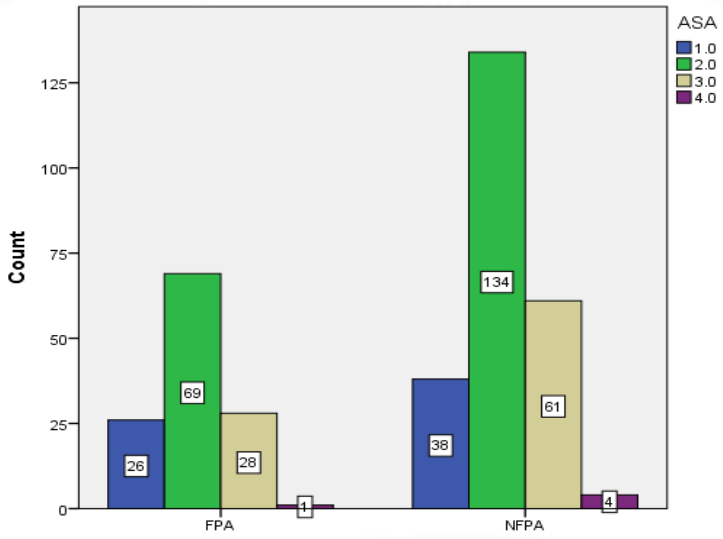
Preoperative tumour volume was 23.69 cm^3 for group 1 and 21.01 cm^3 for group 2 (p=0.408). Group 1 comprised of 38.3% of functioning pituitary adenomas and 61.7%

of non- functioning pituitary adenomas, whereas group 2 comprised of 22.8% functioning pituitary adenomas and 77.2%of non- functioning pituitary adenomas **(p=0.07).** Distribution in relation to ASA grade in comparable in both the groups. (Graph 3 and 4, Table 3)

Graph 3: Bar diagram showing distribution of functioning pituitary adenomas (FPA) and non-functioning pituitary adenomas in (NFPA) the two groups



Graph 4: Bar diagram showing distribution of functioning pituitary adenomas (FPA) and non-functioning pituitary adenomas in (NFPA) the two groups in relation to ASA grades



Cardiology clearance for surgery: A mild and moderate cardic risk for surgery was seen in 26.1% of patients belonging to group 2(>60years) and they had higher Charlson's score with mean Charlson's score of 5.78 and higher frailty index with mean frailty index of 0.1514 and had higher ASA grade of ASA grade II or ASA grade III **(p=<0.001).**

Table 3: Comparison of preoperative presentation in the two groups

Variables	Category	Group 1(n=269)		Group 2(n=92)		P-Value
		n	%	n	%	
Sex	Male	125	46.47%	49	53.26%	0.260
	Female	144	53.53%	43	46.74%	
Presenting complaints	Positive pressure symptoms	223	82.90%	80	86.96%	0.360
	Visual disturbances	212	78.81%	78	84.78%	0.213
	Headache	149	55.39%	46	50.00%	0.371
	Menstrual complaints	24	8.92%	0	0%	**0.003***
	Apoplexy	17	6.31%	7	7.61%	0.668
	Seizures	3	1.11%	0	0%	0.309
	Altered sensorium	3	1.11%	3	3.26%	0.165
	Loss of consciousness	2	0.74%	1	1.09%	0.754
	Cranial nerve deficits	8	2.97%	4	4.35%	0.526
	Limb weakness	6	2.22%	1	1.09%	0.492
Duration	Mean duration of symptoms (in months)	20.05	NA	16.50	NA	0.298
Clinical examination	Visual acuity deficits	224	83.27%	85	92.39%	**0.032***
	Visual field deficits	212	78.81%	82	89.13%	**0.028***
	Extraocular muscle Palsy	12	4.46%	6	6.52%	0.433
	CVS complaints like palpitation, anxiety	61	22.68%	31	33.70%	**0.031***
	Features of Hypopituitarism	92	34.20%	15	16.30%	**0.001***
	Cranial nerve palsies	13	4.83%	7	7.6%	0.315
	Limb weakness	7	2.60%	3	3.26%	0.740
	Loss of secondary sexual characteristics	4	1.49%	1	1.09%	0.777
Imaging	Mean tumor volume on MRI(cm^3)	23.69	NA	21.01	NA	0.408
Type of adenoma	Functioning PA	103	38.3%	21	22.8%	**0.07***
	Non-functioning PA	166	61.7%	71	77.2%	

* = Statistically Significant
CVS = cardiovascular system

Operative outcome:

The mean duration of surgery for group 1 was 3.7 hours and for group 2 was 3.4 hours **(p 0.075).** The extent of resection (EOR) for both groups was also comparable and majority underwent gross total rection (94.1% in group 1 and 94.6% in group 2). Gross total resection achieved in patients with low charlson's score and lower frailty index. Patient who underwent partial resection had higher charlson's score and higher frailty index. Patients who underwent gross total resection were of ASA grade 1 and patient with partial resection were of higher ASA grade (ASA 2 and ASA 3, p=0.846)

Total of 129/361 patients had intra operative CSF leak. The incidence of intra-operative CSF leak was slightly higher in group 2, and it's statistically not significant (group-1 34.2% and group-2 40.2%, p=0.299). Charlson's score and frailty index were comparable in both groups, and patients with intra-operative CSF leak were of higher ASA grade (ASA 2 and ASA 3, p=0.613).

Intraoperative carotid injury was more in group 2(group 2 - 3.3%, group 1 0.4%, **p=0.022**) and the patient with carotid injury had higher charlson's score with a mean charlson's score of 5.667 with comparable frailty index and were of higher ASA grade (ASA 2 and ASA 3, p=0.516).

Intraoperative cranial nerve injury was seen in only one patient who belongs to group 1 and the same patient had intra operatively profuse bleed, for which nasal packing was done as it was not controllable. Later on digital subtraction angiogram (DSA) found to have left cavernous ICA pseudoaneurysm and it was coiled. Later check DSA

found persistent flow, nasal pack removed and as bleeding was not stopped- ICA was ligated. This patient was of age 49 years, with ASA grade 2, with charlson's score of 4 and frailty index of 0.12, who was diabetic and hypertensive.

Table 4: Comparison of duration of surgery and duration of hospital stay in the two groups

Operative outcomes	**Category**	**Group 1(n=269)**	**Group 2(n=92)**	**P-Value**
Duration	Mean duration of surgery(in hours)	3.7	3.4	**0.075***
	Mean duration total hospital stay(in days)	14.292	15.330	0.215
	Mean duration post op hospital stay(in days)	10.511	8.516	0.671

Table 5: **Comparison of intraoperative events in the two groups**

		Group 1(n=269)		Group 2(n=92)		
Operative outcomes	Category	n	%	n	%	P-Value
Extent of resection	Gross total resection	253	94.1%	87	94.6%	0.959
	Near total resection	12	4.5%	4	4.3%	
	Partial resection	4	1.5%	1	1.1%	
Intra op CSF leak	Yes	94	34.9%	35	38.0%	0.592
	No	175	65.1%	57	62.0%	
Intra op carotid injury	Yes	1	0.4%	3	3.3%	**0.022***
	No	268	99.6%	89	96.7%	
Intra op cranial nerve injury	Yes	1	0.4%	0	0%	0.558
	No	268	99.6%	92	100%	

Complications:

The incidence of post operative CSF rhinorrhea for group 1 was 16.7% and for group 2 was 14.1%, p=0.58). The association of Charlson's score and frailty index with CSF rhinorrhea were comparable in both groups, and patients with CSF rhinorrhea were of higher ASA grade (ASA 2 and ASA 3, p=0.416). Post operative CSF rhinorrhoea was present in total of 58 patients , in which 6 patient's warranted surgical repair, where rest 52 patients managed with either lumbar drain alone or with Diamox (Tablet. Acetazolamide) therapy.

The incidence of postoperative meningitis for group 1 was 2.6% and for group 2 was 2.2% (p=0.82) and charlson's score and frailty index were comparable in both groups. Though statistically not significant the incidence of postoperative meningitis more in patients with higher ASA grade (ASA 2 and ASA 3, p=0.470)

The incidence of post-operative diabetes insipidus (DI) for group 1 was 16.7% and for group 2 was 20.7% (p=0.395). Patient with DI had higher charlson's score (mean charlson's score- 5.211, p=0.165) and higher frailty index (mean frailty index – 0.1116, p=0.95) compared to patients without DI. Patients with DI were of higher ASA grade (ASA 2 and ASA 3, p=0.638)

The incidence of post-operative diplopia for group 1 was 1.5% and for group 2 was 1.1% (p=0.777). Though statistically not significant, patient with diplopia had higher charlson's score (mean charlson's score- 3.25, p=0.742) and higher frailty index (mean

frailty index – 0.09, p=0.175) compared to patients without diplopia. Patients with post-operative diplopia were of higher ASA grade (ASA 2 and ASA 3, p=0.554)

The incidence of relatively for group 1 was 2.30% and for group 2 was 2.20% (p=0.754). Patient with Visual deterioration had relatively higher charlson's score (mean charlson's score- 3.624, p=0.804) and relatively higher frailty index (mean frailty index – 0.0950, p=0.506) compared to patients without relatively. Patients with relatively were of higher ASA grade (ASA 2 and ASA 3, p=0.762)

Table 6: Comparing incidence of post operative complications in two groups

Complications	Category	Group 1(n=269)		Group 2(n=92)		P -value
		n	%	n	%	
CSF rhinorrhoea	Yes	45	16.7%	13	14.1%	0.558
	No	224	83.3%	79	85.9%	
Diabetes insipidus	Yes	45	16.7%	19	20.7%	0.395
	No	224	83.3%	73	79.3%	
Post op meningitis	Yes	7	2.6%	2	2.2%	0.820
	No	262	97.4%	90	97.8%	
Diplopia	Yes	4	1.5%	1	1.1%	0.777
	No	265	98.5%	91	98.9%	
Visual deterioration	Yes	6	2.30%	2	2.20%	0.754
	No	263	97.70%	90	97.80%	

Post op outcomes

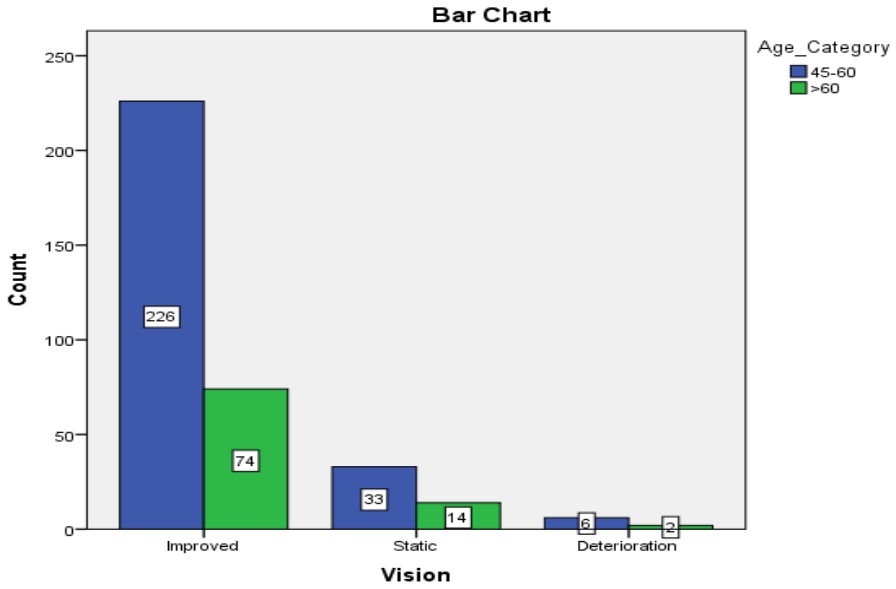
The incidence of post-operative residual volume was comparable in both groups, where in group 1 86.2% with no residue, 8.9% with small residue and 4.8% with gross residue and for group 2, 88% with no residue, 8.7% with small residue and 3.3% with gross residue (p =0.814). Charlson's score and frailty index were comparable in both

groups and patients with gross residue were of higher ASA grade (ASA 2 and ASA 3, p=0.166)

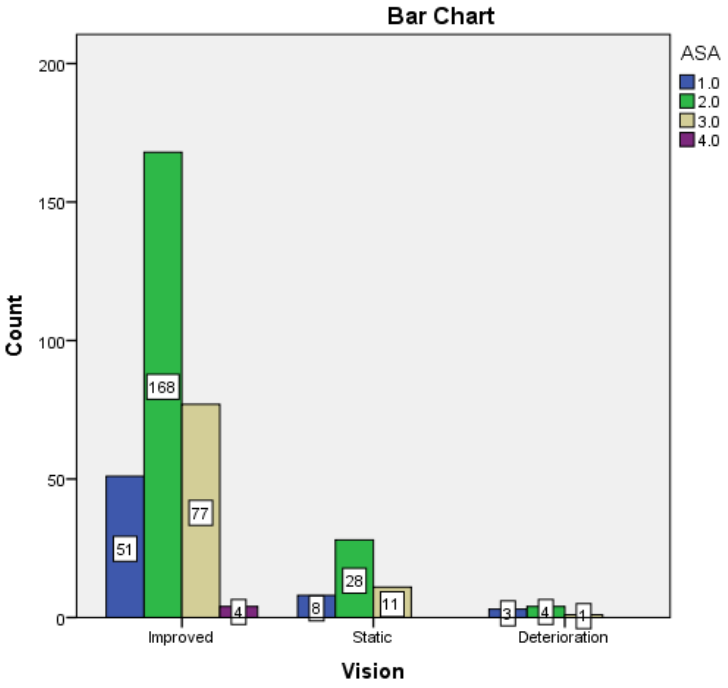
Table 7: Comparing incidence of post operative outcomes in two groups

Post op outcomes	Category	Group 1(n=269)		Group 2(n=92)		P-Value
		n	%	n	%	
Residual volume	No residue	232	86.2%	81	88.0%	0.814
	Small residue	24	8.9%	8	8.7%	
	Gross residue	13	4.8%	3	3.3%	
Vision	Improved	226	85.30%	74	82.20%	0.754
	Static	33	12.50%	14	15.60	
	Deterioration	6	2.30%	2	2.20%	
Need for resurgery	Yes	29	10.78%	3	3.3%	**0.029***
	No	240	89.21%	89	96.7%	
Indication for resurgery	Recurrence/ residue	11	4.09%	13	14.13%	**0.003***
	CSF rhinorrhea	4	1.49%	2	2.17%	0.656
	Carotid injury	1	0.37%	0	0%	0.558
	Intraventricular bleed	1	0.37%	0	0%	0.558
Need for radiotherapy	Yes	6	2.2%	1	1.1%	0.492
	No	263	97.8%	91	98.9%	
Deaths	Yes	4	1.5%	2	2.2%	0.656
	No	265	98.5%	90	97.8%	

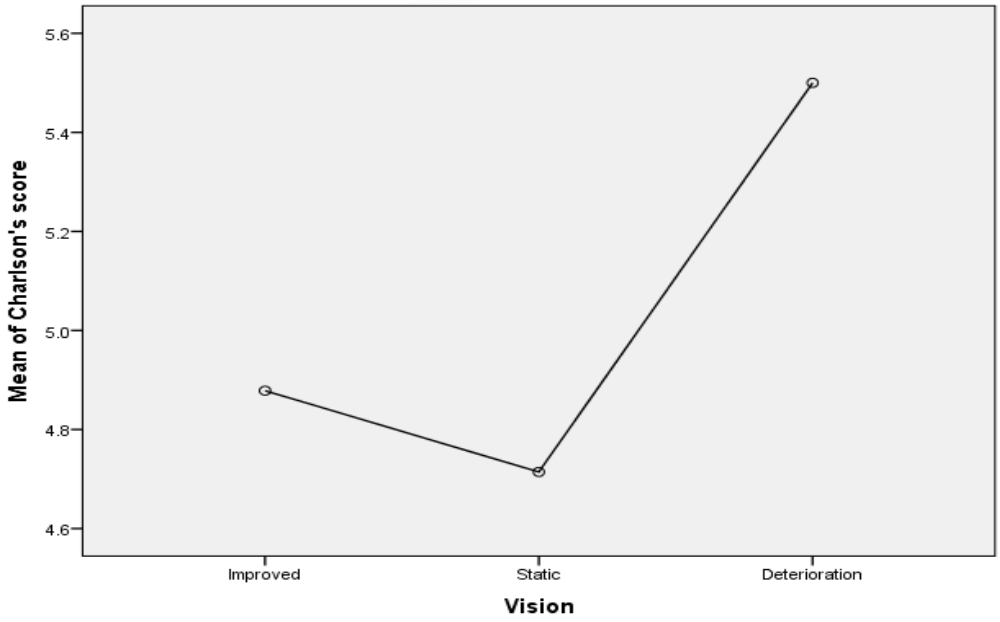
Graph 5: Bar diagram showing status of postoperative vision improvement in the two groups



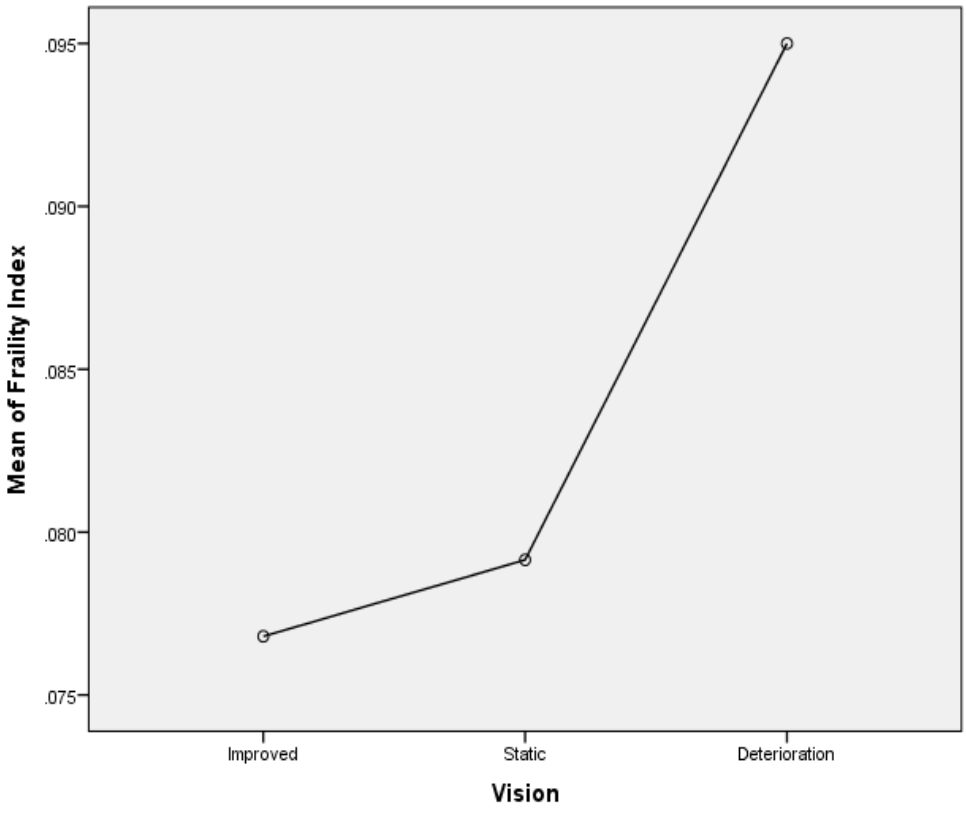
Graph 6: Bar diagram showing status of postoperative vision improvement in the two groups in relation to ASA grades



Graph 7: Graph showing status of postoperative vision status in relation to charlson's score



Graph 8: Graph showing status of postoperative vision status in relation to frailty index



Re surgery

Among total 361 patients, 32 patients underwent 2nd surgery. Group 1 - 29 patients (10.78%) and group 2 – 3 (3.3%) patients underwent 2nd surgery (p=0.35). Charlson's score and frailty index were comparable in both groups of patients who warranted resurgery and who didn't. But patients who underwent resurgery were of higher ASA grade (ASA 2 and ASA 3, p=0.696)

Indications of resurgery were

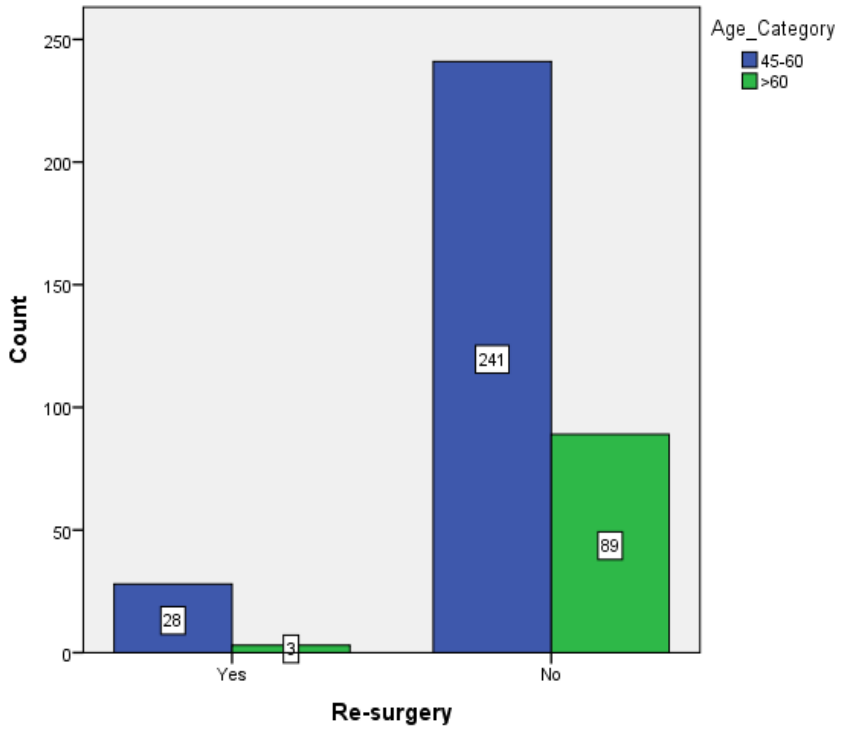
1. Recurrence /residue – 24 (75.00%)
2. CSF rhinorrhea – 6(18.00%)
3. Carotid injury – 1(3.12%)
4. Intraventricular bleed- 1(3.12%)

Table 8: Comparison of association of patients who underwent resurgery with Age, ASA grade, Charlson's score and Frailty index

Comorbidity scores	Category	Resurgery (n=32)		No Resurgery (n=329)		P-value
		n	%	n	%	
Age	Group 1:45-60yrs(n=269)	29	10.78%	240	89.21%	**0.029***
	Group 2:>60 yrs (n=92)	3	3.3%	89	96.7%	
ASA grade	ASA Grade I	5	1.39%	59	16.34%	0.696
	ASA Grade II	16	4.43%	187	51.80%	
	ASA Grade III	10	2.77%	79	21.88%	
	ASA Grade IV	0	0%	5	1.39%	
Charlson's comorbidity index(CCI)score	Mean CCI score	3.290	NA	3.555	NA	0.299
Frailty index	Mean frailty index	.0723	NA	.0784	NA	0.468

* = Statistically Significant, NA= not applicable

Graph 9: Bar diagram showing distribution of patients who warranted resurgery in the two groups



Post operative Radiotherapy:

Total 7 (1.9%) out of 361 patient received post op radiotherapy. And 5 out of these 7 (71.42%) patients had functioning pituitary adenoma (FPA) and 2 patients had non-functioning pituitary adenoma (NFPA) (**p = 0.037**). Among 5 functioning pituitary adenomas, 3 were growth hormone secreting adenomas and 2 were cortocotrophin adenoma. Surprisingly all the 7 patient who warranted radiotherapy underwent gross total resection during primary surgery. The indications for radiotherapy was invasive pituitary adenoma in 3 out of 7 patients and recurrence/residue in 4 out of 7 patients. Patients who warranted radiotherapy showed significant recurrence/residue in follow up scan (p = <**0.001**)

Graph 10: Bar diagram showing distribution of patients who warranted post op radiation in the two groups

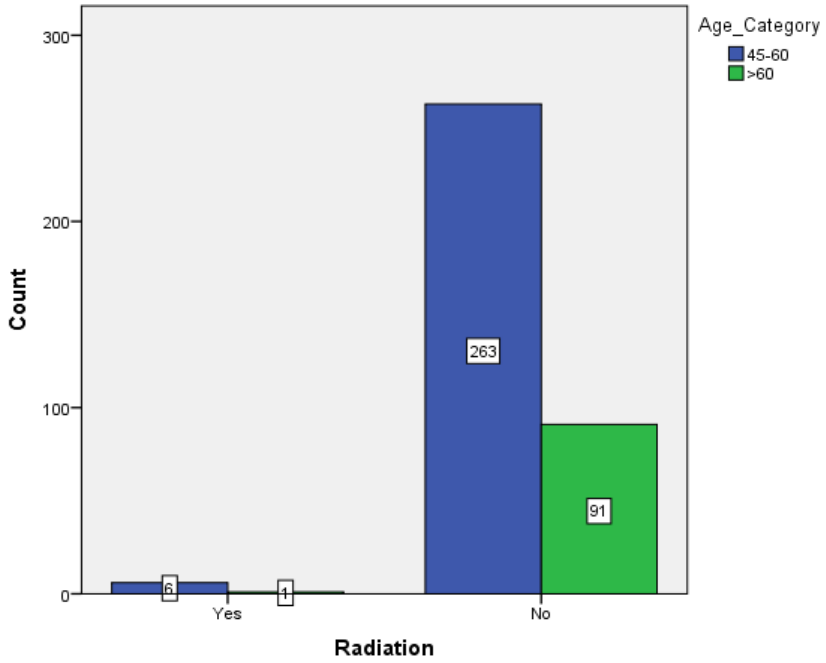


Table 9: Comparison of association need for post operative radiotherapy with extent of resection, residual volume, Age, ASA grade, Charlson's score and Frailty index

Comorbidity scores	Category	Radiation (n=7)		No Radiation (n=354)		P-value
		n	%	n	%	
Extent of resection	Gross total resection	7	1.93%	333	92.24%	0.802
	Near total resection	0	0%	16	4.43%	
	Partial resection	0	0%	5	1.39%	
Residual volume	No residue	0	0%	313	86.70%	**<0.001***
	Small residue	3	0.83%%	29	8.03%	
	Gross residue	4	1.11%	12	3.32%	
Histopathology	Functioning PA	5	1.39%	119	32.96%	**0.037***
	Non- Functioning PA	2	0.55%	235	65.10%	
Age	Group 1:45-60yrs(n=269)	6	2.2%	263	97.8%	0.492
	Group 2:>60 yrs (n=92)	1	1.1%	91	98.9%	
ASA grade	ASA Grade I	2	0.55%	62	17.17%	0.696
	ASA Grade II	4	1.11%	199	55.14%	
	ASA Grade III	1	0.03%	88	24.37%	
	ASA Grade IV	0	0%	5	1.39%	
		Mean	**SD**	**Mean**	**SD**	
Charlson's comorbidity index(CCI)score	Group 1:45-60yrs(n=269)	2.67	0.82	3.08	1.08	0.35
	Group 2:>60 yrs (n=92)	4.00	-	4.88	1.20	0.47
Frailty index	Group 1:45-60yrs(n=269)	0.05	0.02	0.07	0.03	0.34
	Group 2:>60 yrs (n=92)	0.16	-	0.11	0.06	0.37
Indication for radiotherapy	Invasive PA	3	42.86%	NA		
	Recurrence/residue	4	57.14%			

NA= not applicable

Inpatient Deaths

Total of 6 died out of 361 (1.66%) operated patients. Among this 4(66.67%) patients belongs to group 1 and 2 (33.33%) patients belongs group 2. Majority of the patients who died had higher charlson's comorbidity score(mean = 4.000, p=0.394), higher ASA grade and comparable frailty index(p=0.674) (table 11). These patients had relatively higher tumor volume and in 5 out of 6 patients gross total resection was achieved. 4 (66.67%) out of 6 patients had intra op CSF leak, 3(50%) patients had DI, 2 patients had AWMI, 1 patient had ARF and 1 patient had TEN.

Cause of death and post of day on which patients died has been summarized in table 10.

Graph 11: Bar diagram showing distribution of inpatient deaths in the two groups

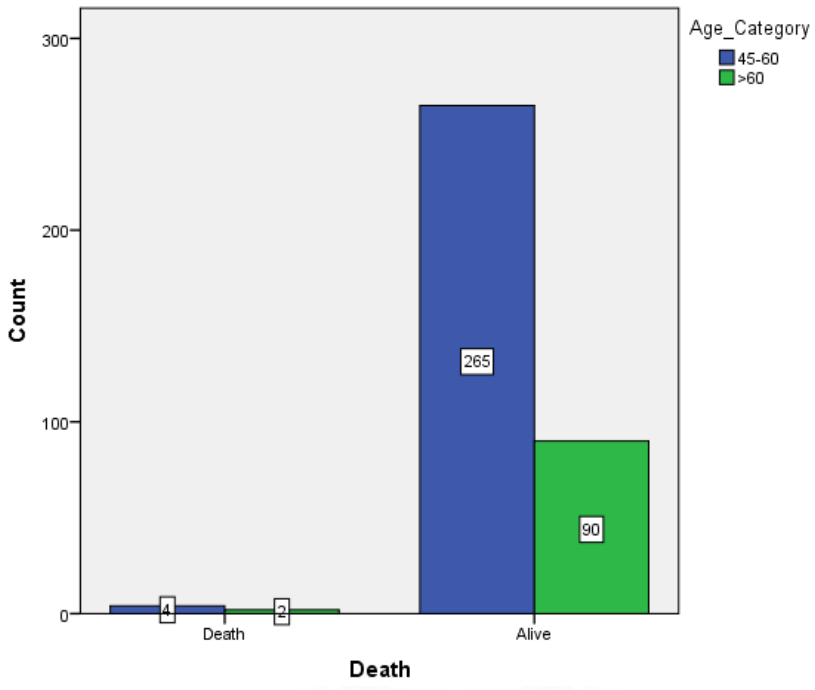


Table 10: Assessment of inpatient deaths with pre and post op parameters

Sl no	Age in year	sex	Primary/ Recurrent	CCI	FI	ASA grade	comorbidities	Tumor volume (cm^3)	EOR	Intra op complication	Post op complication	POD/ Cause of death
1	52	F	Recurrent	9	0.4	4	Uncontrolled DM with end organ failure HTN CAD s/p angioplasty Schizophrenia dementia	24.18	partial	Intra op CSF leak	DI	POD 25 Multiple brain stem infarct
2	53	F	Primary	3	0.04	2	Nil	8.4	Gross total	Intra op CSF leak	Toxic epidermal necrolysis	POD26 Toxic epidermal necrolysis Septic shock
3	69	F	Primary	5	0.16	2	DM HTN	25.66	Gross total	Intra op CSF leak	DI	POD14 AWMI
4	45	M	Primary	2	0.04	1	Nil	10.80	Gross total	Nil	IVH ARF	POD27 ARF
5	65	F	Primary	5	0.12	2	DM	13.88	Gross total	Nil	AWMI	POD9 AWMI
6	57	F	Primary	2	0.04	1	Nil	42.26	Gross total	Intra op CSF leak	DI Fever	POD12 Septic shock

EOR= Extent of resection, POD= post operative day, DI= Diabetes insipidus, DM= Diabetes mellitus, HTN= Hypertension, CAD= Coronary artery disease, IVH= Intraventricular haemorrhage, ARF = acute renal failure, AWMI= Anterior wall myocardial infarction, M= Male, F = Female

Table 11: Comparison of inpatient deaths with Age, ASA grade, Charlson's score and Frailty index

Comorbidity scores	Category	Deaths (n=6)		No deaths (n=355)		p-value
		n	%	n	%	
Age	Group 1:45-60years(n=269)	4	1.5%	265	98.5%	0.656
	Group 2:>60 years (n=92)	2	2.2%	90	97.8%	
ASA grade	ASA Grade I	2	0.55%	62	17.17%	**0.001***
	ASA Grade II	3	0.83%	200	59.8%	
	ASA Grade III	0	0%	89	32.6%	
	ASA Grade IV	1	0.27%	4	1.08%	
Charlson's comorbidity index(CCI)score	Mean CCI score	4.000	NA	3.524	NA	0.394
Frailty index	Mean frailty index	0.0667	NA	0.0781	NA	0.674

5 DISCUSSION

The presence of pituitary adenoma in patients over 60 years old is a relatively common occurrence, with autopsy studies in the elderly and very elderly showing a prevalence of approximately 11– 14%[84]. The incidence of PA increases with age and elderly patients with pituitary adenomas often present with more advanced disease, including visual field defects, compared to their younger counterpart. Previous literature suggest that elderly patients with pituitary adenoma have highly variable range of outcome compare to their younger counterparts. Various studies have been conducted by including patients aged above 60 years. And have shown higher complication rates in elderly population[3,5]. While Sheehan *et al.*[85] and Ferrante *et al.*[86] showed minimal post-operative complications without mortality, Pietila *et al*[87] reported 11% perioperative mortality, and 11% postoperative deterioration following surgery among patients aged from 80 to 86 underwent brain tumour surgery.

The safety and efficacy of neurosurgical intervention for elderly patients with pituitary adenomas, however, has thus far not been fully characterized, potentially complicating the surgical decision making process for such patients and their providers.[888]

We report outcomes on 361 patients with pituitary tumours undergoing endoscopic transnasal pituitary adenoma resection between 2009 and 2021 at our institute and found to have the above mentioned results.

Demography

A total of 361 patients above the age of 45 years were included in the study. These patients were divided into two groups. Group 1 comprising of patients between 45-60 years included 269 (females-144, males-125) patients, and the group 2 comprising of patients aged > 60 years included 92 (females- 43, males- 49) patients.

Associated comorbidities

We have used 3 comorbidity indices to assess patient's preoperative status and to analyze the outcome in relation to associated comorbidities. The 3 comorbidity indices analyzed were ASA grade, Charlson's comorbidity index score and frailty index. Majority of the patient in group 1 belongs to

ASA I and ASA II (208/269, 77.3%) and in group 2 majority of the patients belongs to ASA II and ASA III (85/92, 92.4%). The mean Charlson's score for group 1 was 3.071 and for group 2 was 4.800, which was statistically significant**(p<0.001).** The mean Frailty index for group 1 was 0.0666 and for group 2 was 0.1109, which was statistically significant**(p<0.001).** The Pearson Chi-square value of the comparison was 19.051 with **p value <0.001**. The preoperative Charlson's score showed strong correlation with the ASA grade **(p<0.001)** and Frailty index **(p<0.001). (Table 2).**

Grossman et al[6] showed that greater Charlson score was associated with greater risk of post-operative CSF leak greater risk of post-operative pulmonary complication or fluid and electrolyte disorder etc. and they found that higher Charlson co-morbidity score is an important prognostic factor for inpatients death, length of stay, higher total hospital charge and higher risk of post-operative cerebrospinal fluid leak.

A study by Tomlinson SB et al demonstrated that a novel frailty index based on the National Surgical Quality Improvement Program database was associated with 30-day morbidity and mortality in patients undergoing cranial neurosurgery[10]. Another study by Harland TA et al showed that frailty, as determined by the Hopkins Frailty score, was associated with a higher likelihood of non-home disposition and a longer LOS specifically for brain tumor patients[11]. A recent study by Shahrestani et al. analysed modifiable and nonmodifiable risk factors in patients undergoing pituitary adenoma surgery[12]. Using the Johns Hopkins Frailty Index, the authors found that frail patients had significantly increased hospital LOS, higher total inpatient costs, and higher 90- and 180-day readmission rates when compared to non-frail counterparts. Shahrestani et al. also found that frail patients were significantly more likely to experience acute postsurgical infection compared to nonfrail patients.

Another study by Asemota et al. has examined the predictive value of frailty for cost and LOS for patients undergoing pituitary surgery. Asemota et al. assessed patient frailty in the National Inpatient Sample database using the binary "Johns Hopkins Adjusted Clinical Groups" tool, and determined that frail patients were likely to have a longer LOS and higher costs than non-frail patients[13].

A recent study by Khalafallah et al demonstrate that mFI-5 score is a significant stepwise prognostic marker for hospital LOS and total hospital charges for patients undergoing endoscopic endonasal pituitary surgery in a US hospital and it emphasizing frailty as a key indicator of post-operative outcomes among pituitary adenoma patients and also demonstrates a growing impetus to integrate frailty into clinical workflows. By better understanding which patients are more likely to require additional care,

hospitals and clinicians can provide more informed patient counselling, improve resource utilization, and implement targeted interventions[14].

Four retrospective studies on elderly patients with intracranial meningiomas (305 patients) reported postoperative mortality as the primary outcome measure. In 3 of these studies, the association of the higher ASA physical status classification scores and mortality was significant.[16,17,18,19]

Another retrospective study on 96 elderly intracranial meningioma patients concluded that a preoperative ASA physical status classification score of III or IV predicts poor outcome, defined as a KPS score of 70 or less at 4-month follow-up.[20]

Two studies by Buang et al and Kourbeti et al has demonstrated the higher preoperative ASA physical status classification scores were associated with an increased incidence of postoperative meningitis and infection rates.[21, 22]

Preoperative presentation:

Positive pressure symptoms was seen in 82.90% patients in group 1 and 86.96% patients in group 2 (p= 0.360). Visual disturbances at presentation was seen in 78.81% (212/269) patients in group 1 and 84.8% (78/92) patients in group 2 (p=0.213). Visual acuity disturbances were present in 83.3% group 1 patients and 92.4% group 2 patients **(p=0.032).** Visual field deficits were seen in 89.1% of patients in group 2 as compared to 78.8% of group 1 patients **(p=0.028).** Visual field defects were seen in 89.1% of group 2 patients as opposed to 78.8% of group 1 patients **(p= 0.028).** The higher

incidence of preoperative visual field defects was seen in patients with a higher Charlson's score of 5-6 (92.6%) and > 6 (92.9%) **(p=0.002).**

Headache was noted in 55.39% patients in group 1 and 50.00% patients in group 2 (p= 0.371). Menstrual complaints was noted in 8.92% patients in group 1 and 0 %patients in group 2, as these patients were above 60 years **(p= 0.003).** Apoplexy was noted in 6.31% patients in group 1 and 7.61% patients in group 2(p=0.668). Seizures was noted in 3 (1.11%) patients in group 1 and none in group 2 (p=0.668). Loss of consciousness was seen in 2 (0.74%) patients in group 1 and 1 (1.09%) patient in group 2 (p=0.754).Cranial nerve deficits were seen in 8 (2.97%) patients in group 1 and 4 (4.35%) in group 2 (p= 0.526). Limb weakness/hemiparesis noted in 6 (2.22%) patients in group 1 and 1 (1.09%) in group 2 (p= 0.492). The incidence of hemiparesis and cranial nerve palsies (4.7%, **p=0.027**) at presentation mainly noted in patients with a higher Charlson's score.

Extraocular muscle Palsy were seen in 12 (4.46%) patients in group 1 and 6 (6.52%) in group 2 (p= 0.433). Cardiovascular complaints like palpitation and anxiety were seen in 61(22.68%) patients in group 1 and 31 (33.70%) in group 2, which was statistically significant (**p= 0.031**).

Features of Hypopituitarism seen in 92(34.20%) patients in group 1 and 15 (16.30%) in group 2, which was statistically significant (**p= 0.001**). Loss of secondary sexual characteristics seen in 4 (1.49%) patients in group 1 and 1 (1.09%) in group 2 (p= 0.777).

Mean duration of symptoms were of 20.05 months in group 1 and 16.50 in group 2 (p= 0.298)

Preoperative tumour volume was 23.69 cm^3 for group 1 and 21.01 cm^3 for group 2 (p=0.408).

Group 1 comprised of 38.3% of functioning pituitary adenomas and 61.7% of non-functioning pituitary adenomas, whereas group 2 comprised of 22.8% functioning pituitary adenomas and 77.2%of non- functioning pituitary adenomas **(p=0.07).** Distribution in relation to ASA grade in comparable in both the groups. (Graph 3 and 4, Table 3)

It was retrospectively found that majority of the patients who were cleared under mild and moderate cardiology risk for surgery belongs to group 2(>60years) and they had higher charlson's score with mean charlson's score of 5.78 and higher frailty index with mean frailty index of 0.1514 and had higher ASA grade of ASA grade II or ASA grade III, which was statistically significant **(p=<0.001).**

Our results in relation to preoperative presentation are comparable with the literature.

Operative outcome:

The mean duration of surgery for group 1 was 3.7 hours and for group 2 was 3.4 hours **(p 0.075).** The extent of resection (EOR) for both groups was also comparable and majority underwent gross total rection (94.1% in group 1 and 94.6% in group 2). Gross total resection achieved in patients with low charlson's score and lower frailty index. Patient who underwent partial resection had higher charlson's score and higher frailty index. Majority of the patients who underwent gross total resection were of ASA grade

I and ASA grade II and patient with partial resection were of higher ASA grade (ASA II and ASA III, p=0.846)

Total of 129 patients out of 361 patients had intra operative CSF leak. The incidence of intra-operative CSF leak was slightly higher in group 2, and it's statistically not significant (group-1 34.2% and group-2 40.2%, p=0.299). Charlson's score and frailty index were comparable in both groups, and though its statistically significant patients with intra-operative CSF leak were of higher ASA grade (ASA 2 and ASA 3, p=0.613).

Intraoperative carotid injury was more in group 2(group 2 - 3.3%, group 1 0.4%, **p=0.022**) and the patient with carotid injury had higher charlson's score with a mean charlson's score of 5.667 with comparable frailty index and were of higher ASA grade (ASA 2 and ASA 3, p=0.516).

Intraoperative cranial nerve injury was seen in only one patient who belongs to group 1 and the same patient had intra operatively profuse bleed, for which nasal packing was done as it was not controllable. Later on, digital subtraction angiogram (DSA) found to have left cavernous ICA pseudoaneurysm and it was coiled. Later check DSA found persistent flow, nasal pack removed and as bleeding was not stopped- ICA was ligated. This patient was of age 49 years, with ASA grade 2, with charlson's score of 4 and frailty index of 0.12, who was diabetic and hypertensive.

Post operative inpatient complications:

The incidence of post operative CSF rhinorrhea for group 1 was 16.7% and for group 2 was 14.1%, p=0.58). The association of Charlson's score and frailty index with CSF rhinorrhea were comparable in both groups, and patients with CSF rhinorrhea were of higher ASA grade (ASA 2 and ASA 3, p=0.416). Post operative CSF rhinorrhoea was present in total of 58 patients , in which 6 patient's warranted surgical repair, where rest 52 patients managed with either lumbar drain alone or with Diamox (Tablet. Acetazolamide) therapy.

The incidence of post-operative diabetes insipidus (DI) for group 1 was 16.7% and for group 2 was 20.7% (p=0.395). Patient with DI had higher charlson's score (mean charlson's score- 5.211, p=0.165) and higher frailty index (mean frailty index – 0.1116, p=0.95) compared to patients without DI. Patients with DI were of higher ASA grade (ASA 2 and ASA 3, p=0.638)

The incidence of postoperative meningitis for group 1 was 2.6% and for group 2 was 2.2% (p=0.82) and charlson's score and frailty index were comparable in both groups. Though statistically not significant the incidence of postoperative meningitis more in patients with higher ASA grade (ASA 2 and ASA 3, p=0.470).

The incidence of visual deterioration relatively for group 1 was 2.30% and for group 2 was 2.20% (p=0.754). Patient with visual deterioration had relatively higher charlson's score (mean charlson's score- 3.624, p=0.804) and relatively higher frailty index (mean frailty index – 0.0950, p=0.506) compared to patients without visual deterioration and these patients relatively had higher ASA grade (ASA 2 and ASA 3, p=0.762)

The incidence of post-operative diplopia for group 1 was 1.5% and for group 2 was 1.1% (p=0.777). Though statistically not significant, patient with diplopia had higher charlson's score (mean charlson score- 3.25, p=0.742) and higher frailty index (mean frailty index – 0.09, p=0.175) compared to patients without diplopia. Patients with post-operative diplopia were of higher ASA grade (ASA 2 and ASA 3, p=0.554).

Grossman et al[6] showed that the overall surgical morbidity and mortality were greater for elderly patients who underwent surgery for PA. Higher number of complications were reported in elderly patient (>60 years) including CSF rhinorrhoea, vascular complication including pseudo aneurysm formation and hypopituitarism.

Post op outcomes

The incidence of post-operative residual volume was comparable in both groups, where in group 1 86.2% with no residue, 8.9% with small residue and 4.8% with gross residue and for group 2, 88% with no residue, 8.7% with small residue and 3.3% with gross residue (p =0.814). Charlson's score and frailty index were comparable in both groups and patients with gross residue were of higher ASA grade (ASA 2 and ASA 3, p=0.166).

Post operative vision improved in 85.3%, static in 12.50% and deteriorated in 2.30% patients of group 1, where as its improved in 82.20% static in 15.60and deteriorated in 2.20% patients of group 2 (p=0.754). though statistically not significant, relatively better post operative vision outcome was seen in younger patients in relation to elderly patients, this is probably because they present to us in progressed stage of the tumor. Patients in whom the vision deteriorated had relatively higher charlson's score (mean charlson's score- 3.624, p=0.804) and relatively higher frailty index (mean frailty

index – 0.0950, p=0.506) compared to patients without visual deterioration and these patients relatively were of higher ASA grade (ASA 2 and ASA 3, p=0.762)

A retrospective study done by Horacio et al[89] to analyse the surgical results of 25 elderly patients with non-functioning pituitary macroadenoma operated by the endoscopic endonasal approach. Preoperative visual loss was found in 92.8% of the cases, and 70.8% experienced visual improvement following surgery. Statistical analysis showed no relation between total tumor resection and postoperative visual improvement (p = 0.151).

Re surgery

Among total 361 patients, 32 patients underwent 2nd surgery. Group 1 - 29 patients (10.78%) and group 2 – 3(3.3%) (p=0.35). Charlson's score and frailty index were comparable in both groups of patients who warranted resurgery and who didn't. But patients who underwent resurgery were of higher ASA grade (ASA 2 and ASA 3, p=0.696)

Indications of resurgery were

1. Recurrence /residue – 24 (75.00%)
2. CSF rhinorrhea – 6(18.00%)
3. Carotid injury – 1(3.12%)
4. Intraventricular bleed- 1(3.12%)

A retrospective study done by Horacio et al[89] to analyze the surgical results of 25 elderly patients with non-functioning pituitary macroadenoma operated by the endoscopic endonasal approach, showed that recurrences were observed in only 21.4% of the patients despite a 69.2% rate of subtotal and partial tumor resection. five patients with partial tumor resection and one with subtotal tumor resection presented regrowth of tumor remnants on MRI, which we considered as recurrence. Three patients were operated upon again; no signs of recurrence were observed in two of these patients after five years of follow-up. One patient who presented recurrence of the tumor seven months after the second surgery received radiotherapy. Another two patients received radiotherapy to treat recurrences of a stable tumor remnant after three years of follow-up. One female patient who showed signs of recurrence on MRI five years after surgery without visual loss and at the age of 84 years refused further treatment.

Post operative Radiotherapy:

Total 7 (1.9%) out of 361 patient received post op radiotherapy. And 5 out of these 7 (71.42%) patients had functioning pituitary adenoma (FPA) and 2 patients had non-functioning pituitary adenoma (NFPA)(**p = 0.037**). Among 5 functioning pituitary adenomas, 2 were growth hormone secreting adenomas, 2 were gonadotrophin adenomas and 1 was cortocotrophin adenoma. Surprisingly all the 7 patient who warranted radiotherapy underwent gross total resection during primary surgery. The indications for radiotherapy were invasive pituitary adenoma in 3 out of 7 patients and recurrence/residue in 4 out of 7 patients. Patients who warranted radiotherapy showed significant recurrence/residue in follow up scan (p = <**0.001**)

A study done by Lee CC et al showed that stereotactic radiosurgery (SRS) affords a reasonable rate of endocrine remission in patients with acromegaly and generally does so with a low rate of adverse effects, and growth hormone-secreting tumours may have the best response, although the response is delayed for many years[50]

Inpatient Deaths

Total of 6 died out of 361 operated patients. Among this 4(66.67%) patients belongs to group 1 and 2 (33.33%) patients belongs group 2. Majority of the patients who died had higher charlson's comorbidity score(mean = 4.000, p=0.394), higher ASA grade and comparable frailty index(p=0.674) (table 11). These patients had relatively higher tumor volume and in 5 out of 6 patients gross total resection was achieved. 4 (66.67%) out of 6 patients had intra op CSF leak, 3(50%) patients had DI, 2 patients had AWMI, 1 patient had ARF and 1 patient had TEN.

Cause of death: two patients died of anterior wall myocardial infarction on POD9 and POD 14, 3rd patient died of multiple brain stem infarct on POD 25, 4th patient died of acute renal failure on POD 27, 5th patient died of Toxic epidermal necrolysis and septic shock on POD 26 and 6th patient died of septic shock and multi organ dysfunction on POD 12.

Literature says that in recent years, the complication rates in centres of excellence in pituitary surgery are a mortality of approximately 1%, major morbidity approximately 3% and lesser morbidity approximately 5%[57]. These results are comparable with our study results.

We are expecting our study adds to the knowledge about anticipated complication and outcome according to age group, which helps in the better planning and management of patients based on age and associated comorbidities and helps in pre operative counselling and explaining the possible outcome to patients and their relatives. And we are also hoping to develop a new prognosticating scoring system in future which is tailor made particularly for transnasal endoscopically operated pituitary adenoma cases.

6 SUMMARY AND CONCLUSIONS

Our study suggests that surgery should be the first line of treatment for non-functioning pituitary macroadenomas in the elderly. Patients should be selected for surgical treatment based on their symptoms and clinical condition. Age alone does not determines, rather associated comorbidities and frailty of the patient at the time of surgery which determines surgical outcome and associated perioperative morbidity and mortality. Radical tumor resection should not be the goal in the case of an elderly patient with an non-functioning pituitary macroadenoma as the visual improvement is not related to total tumor resection and recurrences are low even with incomplete resections. Hence endoscopic transnasal excision is a safe treatment modality among patients with pituitary adenoma up to eighth decade of life. ASA grade, Charlson comorbidity index score and frailty index are an important prognosticating factors in determining visual outcome, length of hospital stay, intra op carotid injury, inpatients death, risk of post-operative CSF rhinorrhea and diabetes insipidus.

CONFLICT OF INTEREST : No conflict of interest

7 REFERENCES

1. Srivastava A, Sreejayan K, Joseph AM, Sharma PSVN. Indian research on comorbidities. Indian J Psychiatry 2010; 52:S246–9.
2. Census of India: Age Structure And Marital Status [Internet].[cited 2020 Apr 26]; Available from: http://censusindia.gov.in/Census_And_You/age_structure_and_marital_statuaspx
3. Minniti G, Jaffrain-Rea M-L, Esposito V, Santoro A, Moroni C, Lenzi J, et al. Surgical Treatment and Clinical Outcome of GH-Secreting Adenomas in Elderly Patients. Acta Neurochir (Wien) 2001;143:1205–11.
4. Wilson PJ, Omay SB, Kacker A, Anand VK, Schwartz TH. Endonasal endoscopic pituitary surgery in the elderly. J Neurosurg 2018;128:429–36.
5. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea M-L. Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur J Endocrinol 2005;153:723–35.
6. Grossman R, Mukherjee D, Chaichana KL, Salvatori R, Wand G, Brem H, et al. ORIGINAL ARTICLE: Complications and death among elderly patients undergoing pituitary tumour surgery: Pituitary surgery in the elderly. Clin Endocrinol (Oxf) 2010;73:361–8.

7. Charlson Comorbidity Index (CCI) [Internet]. Mdcalc [cited 2020 Apr 26]; Available from: https://www.mdcalc.com/charlson-comorbidity-index-cci

8. Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-Factor Modified Frailty Index Using American College of Surgeons NSQIP Data. J Am Coll Surg. 2018 Feb;226(2): 173-181.e8. doi: 10.1016/j.jamcollsurg.2017.11.005. Epub 2017 Nov 16. PMID: 29155268.

9. Peña, F.G., Theou, O., Wallace, L. *et al.* Comparison of alternate scoring of variables on the performance of the frailty index. *BMC Geriatr* **14,** 25 (2014). https://doi.org/10.1186/1471-2318-14-25

10. Tomlinson SB, Piper K, Kimmel KT, Vates GE (2017) Preopera- tive frailty score for 30-day morbidity and mortality after cra- nial neurosurgery. World Neurosurg 107:959–965. https://doi. org/10.1016/j.wneu.2017.07.081

11. Harland TA, Wang M, Gunaydin D et al (2020) Frailty as a predictor of neurosurgical outcomes in brain tumor patients. World Neurosurg 133:e813–e818. https://doi.org/10.1016/j. wneu.2019.10.010

12. Shahrestani S, Ballatori AM, Chen XT et al (2020) Analy- sis of modifiable and nonmodifiable risk factors in patients undergoing pituitary surgery. J Neurosurg. https://doi. org/10.3171/2020.4.JNS20417

13. Asemota AO, Gallia GL (2020) Impact of frailty on short- term outcomes in patients undergoing transsphenoidal pituitary surgery. J Neurosurg 132(2):360–370. https://doi. org/10.3171/2018.8.JNS181875

14. Khalafallah AM, Shah PP, Huq S, Jimenez AE, Patel PP, London NR Jr, Hamrahian AH, Salvatori R, Gallia GL, Rowan NR, Mukherjee D. The 5-factor modified frailty index predicts health burden following surgery for pituitary adenomas. Pituitary. 2020 Dec;23(6): 630-640. doi: 10.1007/s11102-020-01069-5. PMID: 32725418.

15. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system

16. D'Andrea G, Roperto R, Caroli E, Crispo F, Ferrante L. Thirty-seven cases of intracranial meningiomas in the ninth decade of life: our experience and review of the literature. Neurosurgery 2005;56:956–61

17. Sacko O, Sesay M, Roux FE, Riem T, Grenier B, Liguoro D, Loiseau H. Intracranial meningioma surgery in the ninth decade of life. Neurosurgery 2007;61:950–4)

18. Schul DB, Wolf S, Krammer MJ, Landscheidt JF, Tomasino Lumenta CB. Meningioma surgery in the elderly: outcome and validation of 2 proposed grading score systems. Neurosurgery 2012;70:555–65

19. Djindjian M, Caron JP, Athayde AA, Février MJ. Intracranial meningiomas in the

elderly (over 70 years old). A retrospec- tive study of 30 surgical cases.
Acta Neurochir (Wien) 1988; 90:121–3)

20. (Cornu P, Chatellier G, Dagreou F, Clemenceau S, Foncin JF, Rivierez M, Philippon J. Intracranial meningiomas in elderly patients. Postoperative morbidity and mortality. Factors pre- dictive of outcome. Acta Neurochir (Wien) 1990;102:98–102

21. Buang SS, Haspani MS. Risk factors for neurosurgical site infections after a neurosurgical procedure: a prospective obser- vational study at Hospital Kuala Lumpur.
Med J Malaysia 2012;67:393–

22. Kourbeti IS, Jacobs AV, Koslow M, Karabetsos D, Holzman RS. Risk factors associated with postcraniotomy meningitis. Neurosurgery 2007;60:317–25

23. Mortini P, Barzaghi R, Losa M, Boari N, Giovanelli M. Surgical treatment of giant pituitary adenomas: strategies and results in a series of 95 consecutive patients. Neurosurgery.2007 ;60:993-1002;

24. Kane LA, Leinung MC, Scheithauer BW et al. Pituitary adenomas in childhood and adolescence. J. Clin. Endocrinol. Metab. 1994; 79: 1135–1140.

25. Ezzat S, Zheng L, Zhu XF, Wu GE, Asa SL. Targeted expression of a human pituitary tumor-derived isoform of FGF receptor-4 recapitulates pituitary tumorigenesis. J. Clin. Invest. 2002; 109 :69–78.

26. Mete, O., Lopes, M.B. Overview of the 2017 WHO Classification of Pituitary Tumors. Endocr Pathol 2017;28, 228–243 .

27. Fleseriu M, Karavitaki N. Non-functioning pituitary adenomas, not all the same and certainly not boring! Pituitary. 2018;21:109–110.

28. Russ S, Anastasopoulou C, Shafiq I. Pituitary Adenoma.In: StatPearls [Internet]. Treasure Island(FL):StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554451/
29. Asa SL, Mete O. A history of pituitary pathology. Endocrine pathology. 2014;25(1):6-11.
30. Balinisteanu B, Ceausu RA, Cimpean AM, Baciu I, Baculescu N, Coculescu M, et al. Conventional examination versus immunohistochemistry in the prediction of hormone profile of pituitary adenomas. An analysis on 142 cases. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie. 2011;52(3 Suppl):1041-5.
31. O'Brien T, O'Riordan DS, Gharib H, Scheithauer BW, Ebersold MJ, van Heerden JA. Results of treatment of pituitary disease in multiple endocrine neoplasia, type I. Neurosurgery. 1996;39(2):273-8; discussion 8-9.
32. Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, et al. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. Science. 2006;312(5777):1228-30
33. Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocrine reviews. 2013;34(2):239-77.
34. Dworakowska D, Korbonits M, Aylwin S, McGregor A, Grossman AB. The pathology of pituitary adenomas from a clinical perspective. Frontiers in bioscience. 2011;3:105-16.
35. Knosp E, Steiner E, Kitz K, Matula C. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery. 1993;33(4):610-7; discussion 7- 8.
36. Biller BM, Swearingen B, Zervas NT, Klibanski A. A decade of the Massachusetts General Hospital Neuroendocrine Clinical Center. The Journal of clinical endocrinology and metabolism. 1997;82(6):1668-74.
37. Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M, et al. UK guidelines for the management of pituitary apoplexy. Clinical endocrinology. 2011;74(1):9-20

38. C.B. W. Neurosurgical managment of large and invasive pituitary tumors. In: F. TGTaCW, editor. Clinical managment of pituitary disorders New York: Raven Press; 1979. p. 335-42
39. Grochowicki M, Vighetto A, Berquet S, Khalfallah Y, Sassolas G. Pituitary adenomas: automatic static perimetry and Goldmann perimetry. A comparative study of 345 visual field charts. The British journal of ophthalmology. 1991;75(4):219-21
40. Guo Q, Young WF, Erickson D, Erickson B. Usefulness of dynamic MRI enhancement measures for the diagnosis of ACTH-producing pituitary adenomas. Clinical endocrinology. 2014.
41. Sharma ST, Raff H, Nieman LK. Prolactin as a marker of successful catheterization during IPSS in patients with ACTH-dependent Cushing's syndrome. The Journal of clinical endocrinology and metabolism. 2011;96(12):3687-94.
42. Molitch ME. Management of incidentally found nonfunctional pituitary tumors. Neurosurgery clinics of North America. 2012;23(4):543-53.
43. Melmed S. Medical progress: Acromegaly. The New England journal of medicine. 2006;355(24):2558-73
44. Carlsen SM, Lund-Johansen M, Schreiner T, Aanderud S, Johannesen O, Svartberg J, et al. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. The Journal of clinical endocrinology and metabolism. 2008;93(8):2984-90.
45. Colao A, Attanasio R, Pivonello R, Cappabianca P, Cavallo LM, Lasio G, et al. Partial surgical removal of growth hormone-secreting pituitary tumors enhances the response to somatostatin analogs in acromegaly. The Journal of clinical endocrinology and metabolism. 2006;91(1):85-92.
46. Schteingart DE. Drugs in the medical treatment of Cushing's syndrome. Expert opinion on emerging drugs. 2009;14(4):661-71.
47. Kienitz T, Quinkler M, Strasburger CJ, Ventz M. Long-term management in five cases of TSH-secreting pituitary adenomas: a single center study and review of the literature. European journal of endocrinology / European Federation of Endocrine Societies. 2007;157(1):39-46
48. Isobe K, Ohta M, Yasuda S, Uno T, Hara R, Machida N, et al. Postoperative radiation therapy for pituitary adenoma. Journal of neuro-oncology. 2000;48(2):135-40.

49. Ciric I, Mikhael M, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. Journal of neurosurgery. 1983;59(3):395-401.
50. Lee CC, Vance ML, Xu Z, Yen CP, Schlesinger D, Dodson B, et al. Stereotactic radiosurgery for acromegaly. The Journal of clinical endocrinology and metabolism. 2014;99(4):1273-81.
51. Ganz JC. Complications of gamma knife neurosurgery and their appropriate management. Acta neurochirurgica Supplement. 2013;116:137-46.
52. Evang JA, Carlsen SM, Svartberg J, Aanderud S, Johannesen O, Schreiner T, et al. [Endogenous Cushing's syndrome]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 2006;126(5):599-602.
53. Rogne SG, Konglund A, Meling TR, Scheie D, Johannesen TB, Ronning P, et al. Intracranial tumor surgery in patients >70 years of age: is clinical practice worthwhile or futile? Acta neurologica Scandinavica. 2009;120(5):288-94.
54. Erfurth EM, Bulow B, Nordstrom CH, Mikoczy Z, Hagmar L, Stromberg U. Doubled mortality rate in irradiated patients reoperated for regrowth of a macroadenoma of the pituitary gland. European journal of endocrinology / European Federation of Endocrine Societies. 2004;150(4):497-502.
55. Musleh W, Sonabend AM, Lesniak MS. Role of craniotomy in the management of pituitary adenomas and sellar/parasellar tumors. Expert review of anticancer therapy. 2006;6 Suppl 9:S79-83.
56. Powell M. Comment. Acta neurochirurgica. 2014;156:449.
57. Thapar KLER. Pituitary tumors: Functioning and nonfunctioning. In: H. RW, editor. Youmans Neurological Surgery. Philadelphia: Saunders; 2004.
58. Rogne SG, Konglund A, Meling TR, Scheie D, Johannesen TB, Ronning P, et al. Intracranial tumor surgery in patients >70 years of age: is clinical practice worthwhile or futile? Acta neurologica Scandinavica. 2009;120(5):288-94
59. Ciric I, Mikhael M, Stafford T, Lawson L, Garces R. Transsphenoidal microsurgery of pituitary macroadenomas with long-term follow-up results. Journal of neurosurgery. 1983;59(3):395-401.
60. Faustini-Fustini M, Pasquini E, Zoli M, Mazzatenta D, Frank G. Pituitary centers of excellence. Neurosurgery. 2013;73(3):E557.

61. Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, et al. A consensus on criteria for cure of acromegaly. The Journal of clinical endocrinology and metabolism. 2010;95(7):3141-8.
62. Newell-Price J. Transsphenoidal surgery for Cushing's disease: defining cure and following outcome. Clinical endocrinology. 2002;56(1):19-21.
63. Chow JT, Thompson GB, Grant CS, Farley DR, Richards ML, Young WF, Jr. Bilateral laparoscopic adrenalectomy for corticotrophin-dependent Cushing's syndrome: a review of the Mayo Clinic experience. Clinical endocrinology. 2008;68(4):513-9.
64. Sanno N, Teramoto A, Osamura RY. Long-term surgical outcome in 16 patients with thyrotropin pituitary adenoma. Journal of neurosurgery. 2000;93(2):194-200.
65. Caton R. NOTES of a CASE of ACROMEGALY TREATED by OPERATION. British medical journal. 1893;2(1722):1421-3.
66. Horsley V. On operative technique of operations on the central nervous system. British medical journal. 1906;2:411-23.
67. Schloffer H. Erfolgreiche Operation eines Hypophysentumors auf nasalem Wege. Wien Klin Wochenschr. 1907;20(621-624).
68. Cushing H. III. Partial Hypophysectomy for Acromegaly: With Remarks on the Function of the Hypophysis. Annals of surgery. 1909;50(6):1002-17.
69. Hirsch O. Endonasal method of removal of hypophyseal tumours: With report of two cases. JAMA. 1910;55:772-4.
70. Liu JK, Das K, Weiss MH, Laws ER, Jr., Couldwell WT. The history and evolution of transsphenoidal surgery. Journal of neurosurgery 2001;95(6):1083-96.
71. Lanzino G, Laws ER, Jr. Pioneers in the development of transsphenoidal surgery: Theodor Kocher, Oskar Hirsch, and Norman Dott. Journal of neurosurgery. 2001;95(6):1097-103.
72. Couldwell WT, Weiss MH, Rabb C, Liu JK, Apfelbaum RI, Fukushima T. Variations on the standard transsphenoidal approach to the sellar region, with emphasis on the extended approaches and parasellar approaches: surgical experience in 105 cases. Neurosurgery. 2004;55(3):539-47; discussion 47-50.

73. Yaniv E, Rappaport ZH. Endoscopic transseptal transsphenoidal surgery for pituitary tumors. Neurosurgery. 1997;40(5):944-6.
74. Cappabianca P, Alfieri A, Colao A, Cavallo LM, Fusco M, Peca C, et al. Endoscopic endonasal transsphenoidal surgery in recurrent and residual pituitary adenomas: technical note. Minimally invasive neurosurgery : MIN. 2000;43(1):38-43.
75. Jho HD, Carrau RL, Ko Y, Daly MA. Endoscopic pituitary surgery: an early experience. Surgical neurology. 1997;47(3):213-22; discussion 22-3.
76. Pasquini E, Sciarretta V, Farneti G, Ippolito A, Mazzatenta D, Frank G. Endoscopic endonasal approach for the treatment of benign schwannoma of the sinonasal tract and pterygopalatine fossa. American journal of rhinology. 2002;16(2):113-8
77. Pergolizzi RS, Jr., Nabavi A, Schwartz RB, Hsu L, Wong TZ, Martin C, et al. Intra-operative MR guidance during trans-sphenoidal pituitary resection: preliminary results. Journal of magnetic resonance imaging : JMRI. 2001;13(1):136-41.
78. Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C. Intraoperative magnetic resonance imaging during transsphenoidal surgery. Journal of neurosurgery. 2001;95(3):381-90.
79. Muskens IS, Zamanipoor Najafabadi AH, Briceno V, Lamba N, Senders JT, van Furth WR, Verstegen MJT, Smith TRS, Mekary RA, Eenhorst CAE, Broekman MLD Visual outcomes after endoscopic endonasal pituitary adenoma resection: a systematic review and meta-analysis. Pituitary. 2017;20:539–552.
80. Qiao, N., Ye, Z., Shou, X., Wang, Y., Li, S., Wang, M., & Zhao, Y. Discrepancy between structural and functional visual recovery in patients after trans-sphenoidal pituitary adenoma resection. Clinical Neurology and Neurosurgery. 2016; 151: 9–17
81. Fahlbusch R , Schott W Pterional surgery of meningiomas of the tuberculum sellae and planum sphenoidale: Surgical results with special consideration of ophthalmological and endocrinological outcomes.J Neurosurg 2002;96:235–243.
82. Zevgaridis D , Medele RJ, Muller A, Hischa AC, Steiger HJ Meningiomas of the sellar region presenting with visual impairment: Impact of various prognostic factors on surgical outcome in 62 patients. Acta Neurochir (Wien) 2002;143:471–476.
83. Margalit NS , Lesser JB, Moche J, Sen C Meningiomas involving the optic nerve: Technical aspects and outcomes for a series of 50 patients. Neurosurgery

2003;53:523–532.

84. Kurosaki, M., Saeger, W. & Ludecke, D.K. (2001) Pituitary tumors in the elderly. Pathology, Research and Practice, 197, 493–497.
85. Sheehan, J.M., Douds, G.L., Hill, K. et al. (2008) Transsphenoidal surgery for pituitary adenoma in elderly patients. Acta Neurochir- urgica, 150, 571–574; discussion 574.
86. Ferrante, L., Trillo, G., Ramundo, E. et al. (2002) Surgical treat- ment of pituitary tumors in the elderly: clinical outcome and longterm follow-up. Journal of Neuro-Oncology, 60, 185–191.
87. Pietila, T.A., Stendel, R., Hassler, W.E. et al. (1999) Brain tumor surgery in geriatric patients: a critical analysis in 44 patients over 80 years. Surgical Neurology, 52, 259–263; discussion 263–254.
88. Eiseman, B. (1996) Surgical decision making and elderly patients. Bull Am Coll Surg, 81, 8–11.
89. Marenco HA, Zymberg ST, Santos Rde P, Ramalho CO. Surgical treatment of non-functioning pituitary macroadenomas by the endoscopic endonasal approach in the elderly. Arq Neuropsiquiatr. 2015 Sep;73(9):764-9. doi: 10.1590/0004-282X20150112. PMID: 26352495.

ANNEXURES

List of publications from Thesis

Appendices

APPENDIX A – TECHNICAL ADVISORY COMMITTEE APPROVAL

APPENDIX B – ETHICS COMMITTEE APPROVAL

APPENDIX C - CURRICULUM VITAE

APPENDIX D – PLAGIARISM CHECK REPORT

APPENDIX A – TECHNICAL ADVISORY COMMITTEE APPROVAL

Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2020/1205 **Date: 09.12.2020**

Project title: RETROSPECTIVE ANALYSIS OF OUTCOMES FOLLOWING ENDOSCOPIC ENDONASAL SURGERY FOR PITUITARY ADENOMA IN ELDERLY POPULATION (> 60 YEARS) IN COMPARISON TO A YOUNGER COHORT (45-60 YEARS)

Principal Investigator:	
Dr Arun Gowda K, Senior Resident, Department of Neurosurgery, SCTIMST	Degree: MBBS, MS
Co-Principal Investigator(s):	
Dr. Prakash Nair, Associate Professor, Department of Neurosurgery, SCTIMST	Degree: MBBS, MS, Mch
Dr Easwer H V, Professor and HOD, Department of Neurosurgery, SCTIMST	Degree: MBBS, MS, MCh
Dr Gohil Jaypalsinh Ashoksigh, Post Doctoral Fellow in skull base surgery, Department of Neurosurgery SCTIMST	Degree: MBBS, MS, MCh

Members who participated in the TAC meeting on 21/11/2020
Dr Harikrishnan S (Chairman)
Dr Manikandan S
Dr Sylaja P N
Dr Narayanan Namboodiri
Dr Sanjay G
Dr Ramshekhar N Menon
Dr Jayanand Sudhir B
Dr Sabarinath Menon
Dr Madhusoodanan U K
Dr Srinivas G (Member Secretary)

Dr Ramshekhar N Menon, Dr Madhusoodanan U K, Dr Jayanand Sudhir B, Dr Manikandan S, Dr Sabarinath Menon and Dr Narayanan Namboodiri (#1189,1201, 1204, 1207, 1208, 1209, 1210, 1213, 1214).

Risk Classification of the project (Minimum/ Moderate/ High): Minimum

Requirement of DSMB: No

Recommended members of DSMB: Not applicable

Recommendations of TAC:
Recommended for consideration of IEC in the light of the responses received from the investigator

The PI may note that there can be no additions / alterations in the documents approved by TAC when they are submitted to the IEC.

Dr Srinivas G

MEMBER SECRETARY
TAC (Clinical Studies)
SCTIMST

Note for IEC
Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

Appendix-1

1. The IEC form should have details of the approximate number of patients planned to be included in the study and the time period during which these patients were operated.

   Answer: Its already mentioned in coloumn

   (F) SUBJECT SELECTION
   (2) Number: Number : Retrospective 300 cases
   (B) TITLE AND DURATION OF PROPOSED STUDY: Duration of the study: Retrospective study from 2005-2021

2. Kindly cross-check whether the prevalence figures stated in the proposal (16.7% in the population; 26% in 45-60 years age group) are correct. Prevalence of 26% means more than one in four of the general population in that age group is affected, a figure too high to be believed. Patient details are provided under patent details

   Answer: What we meant is pituitary adenoma consist of 12.9% of primary intracranial neoplasm with prevalence 16.7% according to western data, among those 16.7% pituitary adenoma cases, 45-60 year age group constitutes 26%, and that's not general population prevalence.

APPENDIX B – ETHICS COMMITTEE APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1761/NOVEMBER/2021 14.01.2022

Dr. Arun Gowda K
Senior Resident
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dear Dr. Arun Gowda,

The Institutional Ethics Committee held on 26th November, 2021, reviewed and discussed your application to conduct the study titled "**RETROSPECTIVE ANALYSIS OF OUTCOMES FOLLOWING ENDOSCOPIC ENDONASAL SURGERY FOR PITUITARY ADENOMA IN ELDERLY POPULATION (>60YEARS) IN COMPARISON TO A YOUNGER COHORT (45-60YEARS)**" (IEC/1761).

The following members of the Ethics Committee were present at the meeting held on 26th November, 2021

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Adv. N Anand	BAL, L LB	Male	Legal Expert	No
6.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
7.	Dr. Achuth Sankar S. Nair	Ph.D (i.Engineering ii.Music)	Male	Social Scientist	No
8.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
9.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.07.2021 from Dr. Arun Gowda, Senior Resident, Department of Neurosurgery, SCTIMST*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.07.2021 from Dr. Prakash Nair, Associate Professor, Department of Neurosurgery, SCTIMST*
4. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.07.2021 from Dr. Easwer HV, Professor and Head, Department of Neurosurgery, SCTIMST*
5. *TAC Approval Letter*
6. *IEC Application Form*
7. *Project Proposal*
8. *List of Abbreviations*
9. *Proforma*
10. *CV of PI and Co-PIs*
11. *Declaration Form*

Revised submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.07.2021 from Dr. Prakash Nair, Associate Professor, Department of Neurosurgery, SCTIMST*
4. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 15.07.2021 from Dr. Easwer HV, Professor and Head, Department of Neurosurgery, SCTIMST*
5. *TAC Approval Letter*
6. *IEC Application Form*
7. *Project Proposal*
8. *List of Abbreviations*
9. *Proforma*
10. *CV of PI and Co-PIs*
11. *Declaration Form*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

PROFORMA FOR DATA COLLECTION

General Instructions
Please fill in all the
questions Write Yes/No
wherever applicable
if no response applies, please write NA
If the response is not known
please write UKIf additional info
is available please elaborate

A . GENERAL INFORMATION

1 Subject code
2 Age
3 Sex
4 Date of admission
5 Date of discharge/death

B.CLINICAL DETAILS

Mode of Presentation
[Visual/apoplexy/headache/hypo-function/hyper-function /incidental/others]

For patients presenting with Positive Symptoms (Headache/Seizures/Apoplexy)Onset of symptom:
Duration of Symptom :
LOC/Altered sensorium & duration :
Seizures :
Cranial nerve defict/Limb weakness (if yes specify):Any other symptoms :
Any specific treatment given :
Improvement in above symptom

For patients presenting with Mass effect
Visual disturbances (if yes specify) Acuity
Visual field
Extra ocular muscle palsies (if yes specify)
Other Cranial nerve deficit (if yes, specify)
Motor weakness (if yes, specify)

Speech disturbance (if yes specify)

Seizures

Endocrinopathy

Clinical features of Hyper/hypopituitarism:

Thyroid/cortisol/ adrenal/gonadal /Prolactin/growth hormone:(specify details)

Secondary sexual characters:

Cardiovascular complaints:

Menstrual complaints:

Examination findings

On admission

GCS

Vitals (BP/PR)

Vision (VA/VF)

Extra ocular movements

Cranial nerve palsy (if yes, specify)

Weakness (if yes, specify)

General examination:

loss of secondary sexual charactersHeight:

weight:

neuro-cutaneous markers:

INVESTIGATIONS

Radiology:

1. CT scan

(Size/site/Extent/Calcification/Vascular relation/bony anatomy)

2. MRI

(Mean Size/Mean height/site/Extent of calcification/Vascular relation/consistency/morphology /contrast enhancement)

Other MRI sequences (details and findings if performed)

3. DSA (relevant finding if performed)

4. Echocardiography findings (relevant findings if performed)

Biochemical:

For Endocrine function(laboratory assessment)

1. Thyroid function test (TSH, fT3, fT4)
2. Growth hormone, Insulin like Growth factor-1 (IGF-l)3.ACTH/Sr. Cortisol (8am)
4. S. Prolactin (in dilution)
5.Gonadal hormones (FSH, LH)
6.Testosterone
7.Urinary cortisol (sample collected over 24 hour)

Any other hormone assessment test performed (please specify)

Surgery

1.Date of surgery

2. Operative time / blood loss
3.Type of approach(endonasal-transsphenoidal/Transethmoidal/transmaxillary)
4. Extent of resection (surgeon's intraoperative impression) (grosstotal/subtotal/biopsy)5.Intra op Events:(CSF leak/carotid injury/Cranial Nerve injury)

Post operative complications:

1.CSF rhinorrhoea (if yes, specify)
2.Meningitis
3.Diplopia :

Follow up:

Clinical:

Clinical follow up:

1) Postoperative:
   Day 1 : CT scan with contrast to assess extent of resection
2) Day 1: S Cortisol 8 am
   Day 4: S Cortisol 8am

3) 3weeks post operative follow up:

3.1) Hormone estimation

S cortisol (8am), Thyroid stimulating hormone (TSH) , S Prolactin

3.2) Endocrinological

need for suppressive medication

Hormonal remission of Functioning tumors

3.2) Visual examination

Visual acuity: Using the Snellen's chart with best uncorrected and corrected visionPerimeter: Using Humphrey's Field Analyzer to assess the visual field chart, Fundoscopy: For assessment of fundus

3.3) any other complications noted on examination:

4) 3 months post operative follow up:

4.1) MRI brain with contrast with postoperative volumetric analysis to look for residual disease

Residual Volume -

4.2) Hormone estimation

S cortisol (8am), Thyroid stimulating hormone (TSH) , S Prolactin

4.3) Endocrinological -

need for suppressive medication

Hormonal remission of Functioning tumors

4.4) Visual acuity: Using the Snellen's chart with best uncorrected and corrected vision

Perimeter: Using Humphrey's Field Analyzer to assess the visual field chart, Fundoscopy: For assessment of fundus

5)6 months post operative follow up:

5.1) Visual acuity:

Using the Snellen's chart with best uncorrected and corrected vision Perimeter: Using Humphrey's Field Analyzer to assess the visual field chart ,

Fundoscopy: For assessment of fundus

6) 1 year post operative follow up

61) MRI imaging of the brain with contrast to look for recurrence or progression of tumour
Residual/ Recurrence Volume-

62) Visual acuity
Using the Snellen's chart with best uncorrected and corrected vision Perimeter: UsingHumphrey's Field Analyzer to assess the visual field chart ,
Fundoscopy: For assessment of fundus

7) Re-surgery
Indications of 2nd operation: (please describe indications in detail)

8)Need adjuvant treatment:
Chemotherapy/Radiotherapy (please describe the indications for adjuvant treatment)

CV of Dr Arun Gowda K

Last Name: Keelara	First Name: Arun	Middle Name: Gowda
Date of Birth (dd/mm/yy): 11/05/1986		Sex: male
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator): Principal Investigator		
Professional Mailing Address(Include Institution name)		Study Site Address (Include Institution name)
SCTIMST, Medical college trivandrum campus,kumarpuram road, trivandrum 695011		SCTIMST, Medical college trivandrum campus, kumarpuram road, trivandrum695011
Telephone (Office): 04712524585		Mobile Number:9731140599
Telephone (Residence):		Email: arungowda15@gmail.com

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MS General surgery	2016-2019	M.S.RAMAIAH MEDICAL COLLEGE, BANGALORE
MBBS	2003-2009	BANGALORE MEDICAL COLLEGE AND RESEARCH INSTITUTE, BANGALORE

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

MBBS Reg no : **85736** (Karnataka medical council), Date of Registration : 19/09/2009
MS Gen surgery Reg no : **85736** (Karnataka medical council), Date of Registration : 03/07/2019
Travancore-Cochin Medical Councils Reg no: **80306**, Date of Registration : 25/10/2021

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Jan 2020-Dec 2022	MCh NEUROSURGERY (AFTER MS) Senior Resident	SCTIMST, Trivandrum

Summary of relevant research experience:

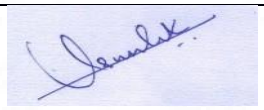
1. Sudhir BJ, **Keelara A. G**, Venkat EH, Kazumata K, Sundararaman A. The mechanobiological theory: a unifying hypothesis on the pathogenesis of moyamoya disease based on a systematic review. *Neurosurg Focus*. 2021;51(3):E6. doi:10.3171/2021.6.FOCUS21281

2. **Keelara A. G**, Satish, C., Rudresh, H.K., Harish, K., & Kapali, A.S. (2021). Rotter's Lymph Nodes—Do We Really Need to Remove During Axillary Clearance? *Indian Journal of Surgical Oncology, 12,* 397 - 400.

3. Gohil J, **Gowda A**, George T, Easwer HV, George A, Nair P. Pituitary apoplexy and panhypopituitarism following acute leptospirosis. *Pituitary*. 2021;24(6):854-858. doi:10.1007/s11102-021-01156-1

4. GC Vilanilam, Nair P, **Keelara A.G**, Easwer HV. Idiopathic intracranial. Hypertension - A ***Surgeon's***. ***Dilemma***. Neurologyindia Jan_Feb_2021. Volume 3, issue 1

5. Sudhir BJ, Arunkumar K, Jamaludeen M A, **Keelara A. G**, strategic tunnelling of superficial temopral artery during bypass surgery for moyamoya disease. Acta Neurochirurgica, December 2021, DOI:10.1007/s00701-021-05084-8

Signature: 	Date: 25/07/2022 Place:Trivandrum

Curriculum vitae of Dr Easwer H V

Last Name: H V	First Name: EASWER	
Date of Birth: (dd/mm/yy) 29/051971		Sex: MALE
Study Site Affiliation: **Co Principal Investigator**		
Professional Mailing Address(Include Institution name)		Study Site Address (Include Institution name)
Professor, Neurosurgery SCTIMST, Trivandrum		Professor, Neurosurgery SCTIMST, Trivandrum
Telephone (Office): 0471 252132		Mobile Number: 9847010577
Telephone (Residence): NIL		Email: easwer@sctimst.ac.in

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
Fellowship in Vascular Neurosurgery	2003-4	SCTIMST, India
MCh Neurosurgery	199-2002	SCTIMST, India
MBBS	1989-96	GMCH, Kottayam, India

Details of professional registration: TCMC 29932, year: 2001

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
2020 July to present	Head of the Department, Neurosurgery	SCTIMST, Trivandrum
2015Aug to present	Professor, Neurosurgery	SCTIMST, Trivandrum
2013 to 2015	Additional Professor	SCTIMST, Trivandrum
2009 to 2014	Associate Professor	SCTIMST, Trivandrum

Brief summary of relevant research experience:
Radiofrequency Thermal Ablation for Trigeminal Neuralgia-operated over 150 cases and published in 2015

Current project(s) at hand: Development of Cerebral Dialysis Catheter
Development of Ceramic Bone substitutes

Signature: 	Date: 25/07/2022 Place: Trivandrum

CV of Dr PRAKASH NAIR

Last Name **NAIR**	First Name **PRAKASH**	Middle Name
Date of Birth (dd/mm/yy) 23/07/1981		Sex Male
Study Site Affiliation: **Co Principal Investigator**		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Dept of Neurosurgery, Sree Chitra Tirunal Institute of Medical Science and Technology. prakashnair@sctimst.ac.in		Sree Chitra Tirunal Institute of Medical Science and Technology. Department of Neurosurgery. Thiruvanathpuram
Telephone (Office):		Mobile Number: 8592833489
Telephone (Residence):		Email- prakashnair@sctimst.ac.in
Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
Mch (Neurosurgery)	2012	Sanjay Gandhi Postgraduate institute, Lucknow, UP
MS	2008	Trivandrum Medical College, Trivandrum, Kerala
MBBS	2002	Govt Medical College, Miraj, Maharashtra
Details of professional registration: (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration Medical council of India, New Delhi. Registration no 25541. Year of registration: 2003 Travancore-Cochin Medical Councils Reg no 38394 (year of registration 2019)		

Current and previous positions (most recent position first):		
Month and Year	Title	Institution/Company, Country
July 2022 - till date	Additional Professor, Dept of Neurosurgery	SCTIMST, Trivandrum
2019 - July 2022	Associate Professor, Dept of Neurosurgery	SCTIMST, Trivandrum
January 2015 – 2019	Assistant Professor, Dept of Neurosurgery	SCTIMST, Trivandrum
Apr 2014-Jan2015	Senior specialist in Neurosurgery	Aster Medcity, Kochi

Brief summary of relevant research experience:

- **Nair P**, Pal L, Jaiswal AK, Behari S: Lhermitte-Duclos disease associated with dysembryoplastic neuroepithelial tumor differentiation with characteristic magnetic resonanceappearance of "tiger striping". World Neurosurgery 75 (5-6):699-703

- **Nair P**, Srivastava AK, Kumar R, Jain K, Sahu RN, Vij M, Jain M: Giant primary intraosseouscalvarial hemangioma of the occipital bone. Neurology India 59 (5):775-776

- Behari S, Jaiswal S, **Nair P**, Garg P, Jaiswal AK: Tumors of the posterior third ventricular regionin pediatric patients: The Indian perspective and a review of literature. Journal of Pediatric Neurosciences 6 (Suppl 1):S56-71-S56-71

- Nair AP, Kumar R, Mehrotra A, Srivastava AK, Sahu RN, **Nair P**: Clinical, radiological profileand outcome in pediatric Spetzler-Martin grades I-III arteriovenous malformations. Child's Nervous System: ChNS: 28 (4):593-598

- **Nair P**, Srivastava AK, Kumar R, Behari S, Jaiswal AK, Sahu RN, Nair AP: Large epidermoids ofthe quadrigeminal cistern: an experience of 15 cases and review of literature. Acta Neurochir , 2012; 154:1391-1398

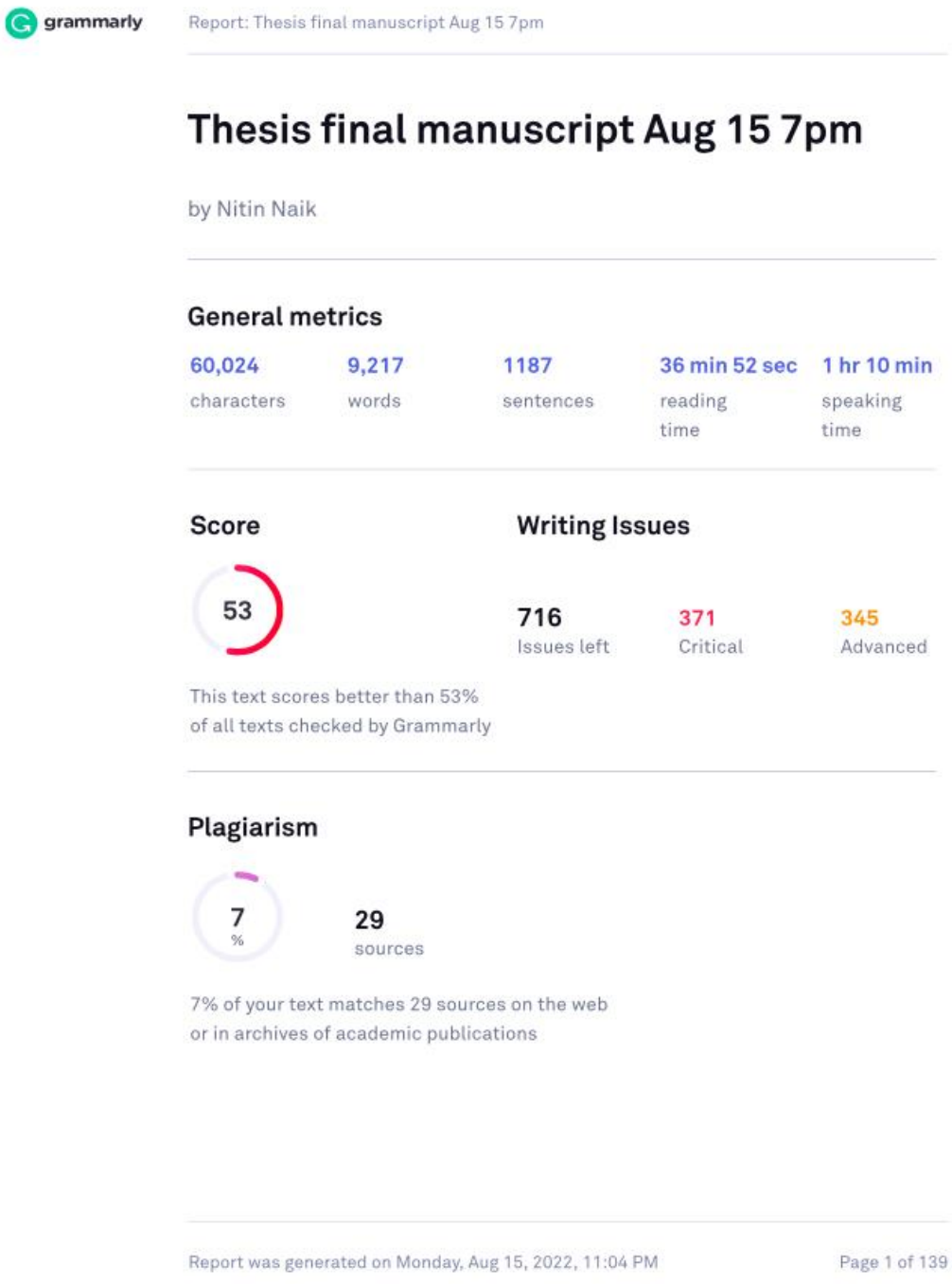
- **Nair P**, Singh DK, Srivastava AK, Kumar R, Behari S, Jaiswal AK, Sahu RN: Hydrocephalus as aprognostic factor in vestibular schwannoma:is preoperative CSF diversion required in vestibular schwannoma? Indian J Neurosurg 2014; 3:19-24

- Das K, **Nair P**, Mehrotra A, et al: Remote cerebellar hemorrhage: Report of 2cases and review of literature. Asian Journal of Neurosurgery. 2014;9(3):161-164.

- **Nair P**, Sardhara J, Kumar A, et al. Deep vein thrombosis in a neurosurgical intensive care: An institutional experience. Indian Journal of Neurosurgery. 2014;3(2):
  93-96.

Current project/s at hand: - 1. “Surgical outcome for endonasal approach to skull base lesions.” 2. “Tumour consistency prediction using magnetic resonance imaging (MRI) in pituitarymacroadenomas to prognosticate visual and endocrine outcome following surgery”	
Signature: 	Date: 25/07/2022 Place: Thiruvananthpuram

APPENDIX D – PLAGIARISM CHECK REPORT



grammarly

Report: Thesis final manuscript Aug 15 7pm

Thesis final manuscript Aug 15 7pm

by Nitin Naik

General metrics

60,024	9,217	1187	36 min 52 sec	1 hr 10 min
characters	words	sentences	reading time	speaking time

Score

53

This text scores better than 53% of all texts checked by Grammarly

Writing Issues

716	371	345
Issues left	Critical	Advanced

Plagiarism

7 %

29 sources

7% of your text matches 29 sources on the web or in archives of academic publications

Report was generated on Monday, Aug 15, 2022, 11:04 PM

Page 1 of 139