

**ANALYSIS OF INTRAOPERATIVE AND RADIOLOGICAL VARIATION OF
CAVERNOUS SINUS INVASION (CSI) IN PITUITARY ADENOMAS (PA)**



Submitted for Post-Doctoral Fellowship

in Skullbase Neurosurgery By

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2023 - 2024

DEPARTMENT OF NEUROSURGERY

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL
SCIENCES & TECHNOLOGY**

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Submitted by: Dr. Sreenath P R

Programme: PDF-Skullbase Neurosurgery

Month & year of submission: December- 2023

DECLARATION

This thesis titled - Analysis of intraoperative and radiological variation of Cavernous Sinus Invasion (CSI) in Pituitary Adenomas (PA) is a consolidated report based on a bonafide study of the period from January 2023 to December 2023, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of the Skullbase Neurosurgery Fellowship examination.

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ACKNOWLEDGEMENT

I owe a deep sense of gratitude to Dr. Krishnakumar K, Professor and Head of the Department of Neurosurgery, for his invaluable advice, inspiration, encouragement, and guidance, without which this work would not have been possible.

The guidance of Dr. Prakash Nair, Additional Professor, Department of Neurosurgery, has been invaluable and I am extremely grateful and indebted for his contributions and suggestions, which were of invaluable help during the entire work. His critical remarks, suggestions, helped me in achieving a high standard of work. He will always be a constant source of inspiration to me.

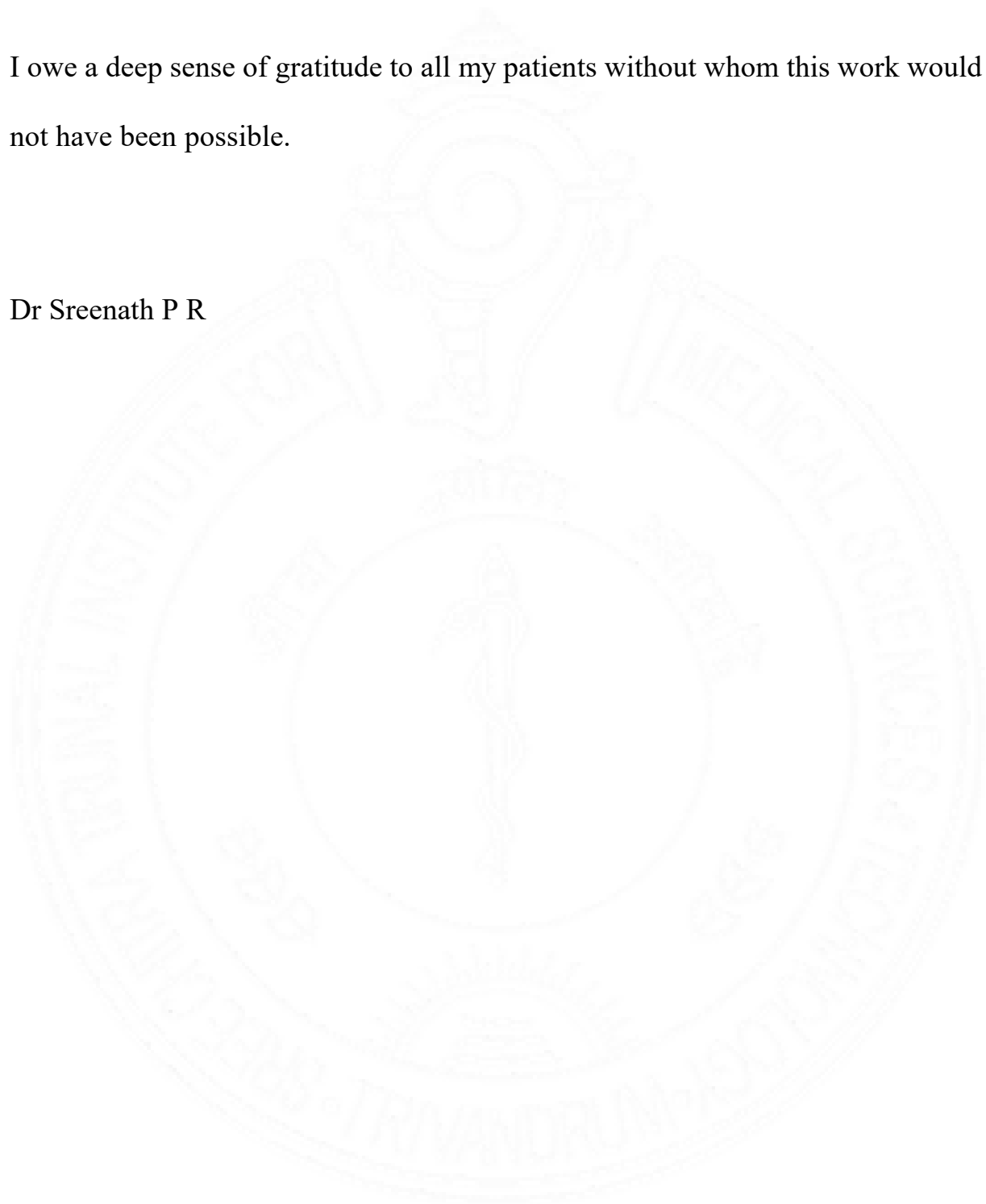
I owe a deep sense of gratitude to Dr. Easwer H V for his invaluable advice, encouragement, and guidance, without which this work would not have been possible. Their critical remarks, suggestions, helped me in achieving a high standard of work.

I am deeply indebted to Dr. Jayanand Sudhir, Dr. Prakash Nair, Dr. Ganesh Divakar, Dr Gowtham M and colleagues and I thank them for their constant

encouragement and support.

I owe a deep sense of gratitude to all my patients without whom this work would not have been possible.

Dr Sreenath P R



OBJECTIVE

CSI by pituitary adenomas form a significant risk factor for incomplete surgical resection.

Whether it is true invasion suggesting an aggressive process or mere opportunistic intrusion into the weak wall of cavernous sinus (CS). Direct intraoperative observation is therefore considered more accurate than radiology in assessment of the integrity of medial wall of CS. The study analyses the correlation between intraoperative finding of CSI and currently existing MRI based classification of CSI.

MATERIALS AND METHODS

Patients who underwent endoscopic trans-nasal transsphenoidal surgery for PAs between 2015 and 2023 were analysed for intraoperative and radiologic correlation.

RESULTS

Of the 312 patients with PAs, Intraoperative CSI was evident in 22.43% patients (n=70). 37.1% of these patients were males. Mean age of presentation was 45.5 ± 12.5 years. Radiological CSI, defined as Knosp grade >2 was noted in 68.57% of these patients (n=48/70). Radiological

interpretation of CSI was less accurate in new cases (n=59) compared to recurrent (n=11) lesions (68.57% vs. 72.7%, p=1.0) whereas, interpretation in non-functional PAs (n=54) were significant compared to functional (n=16) PAs (76% vs. 43.75%, p< 0.0291).

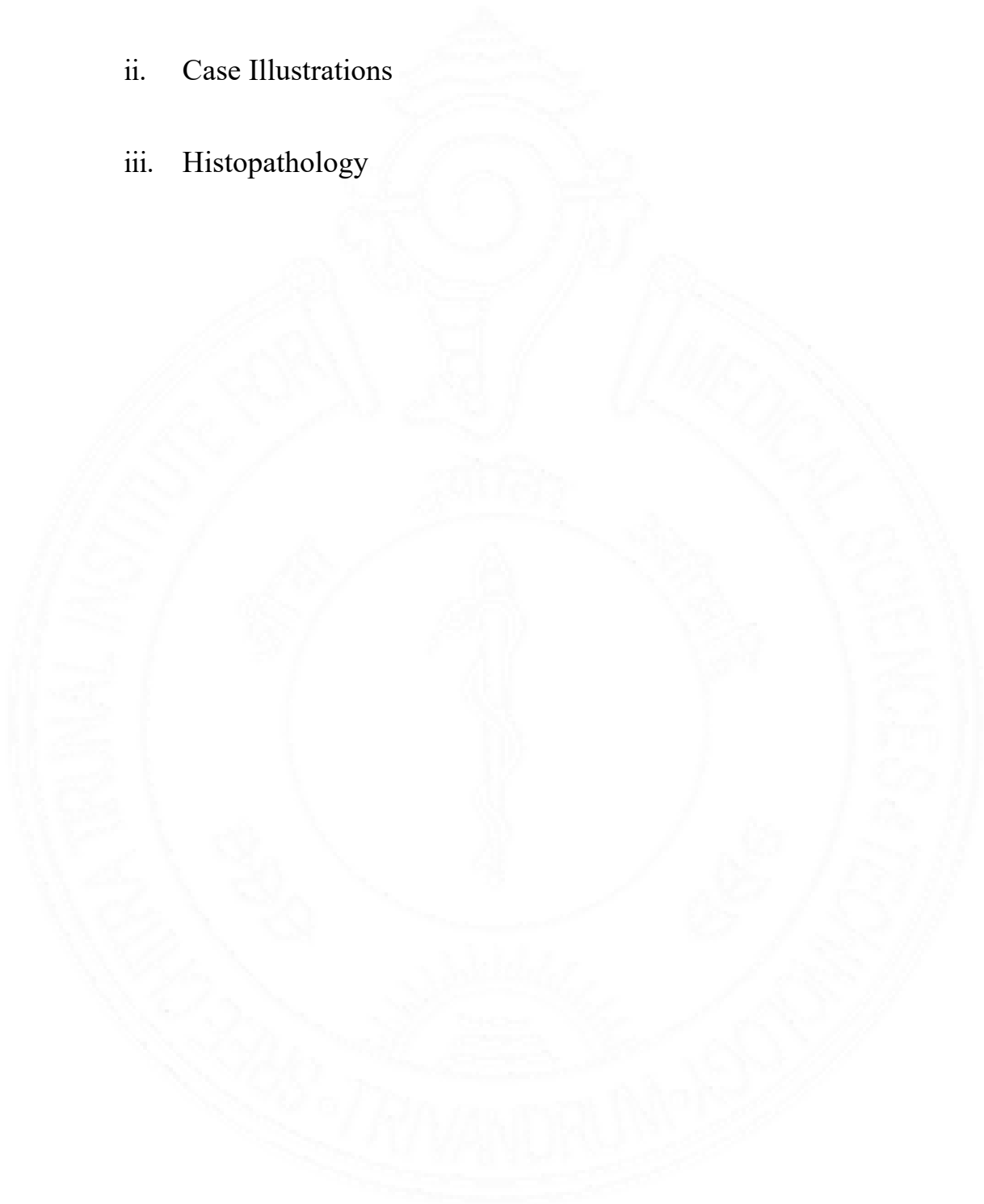
CONCLUSION

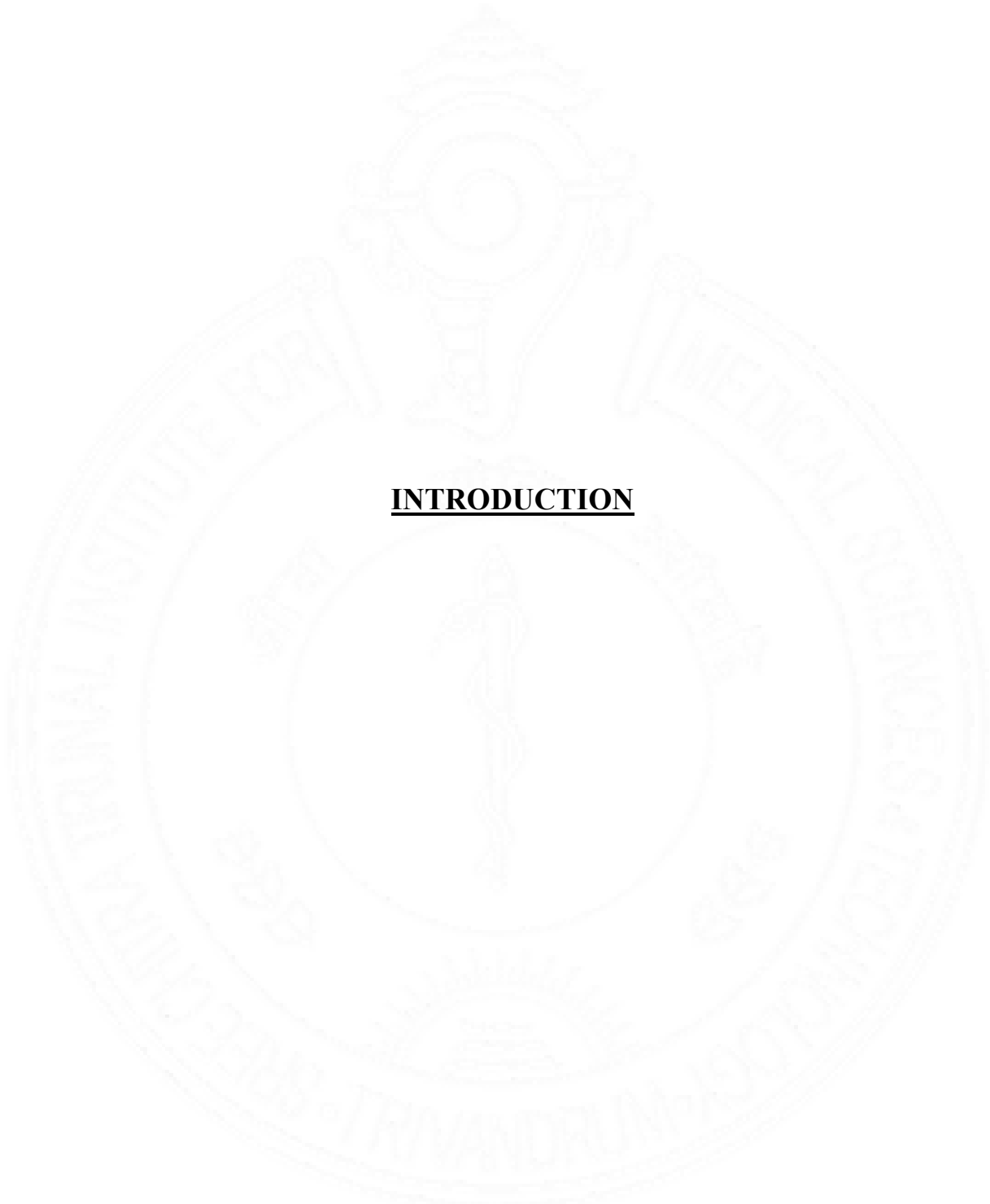
CSI being an important determining factor in extent of resection in endoscopic PA surgeries carries the burden of radiological diagnostic ambiguity. Knosp grading is considered as an excellent tool for prognosticating surgical cure. Although, our data goes in accordance with worldwide reports for direct intraoperative observation (9%-30%), only about two third patients with intraoperative CSI had radiological evidence of the same.

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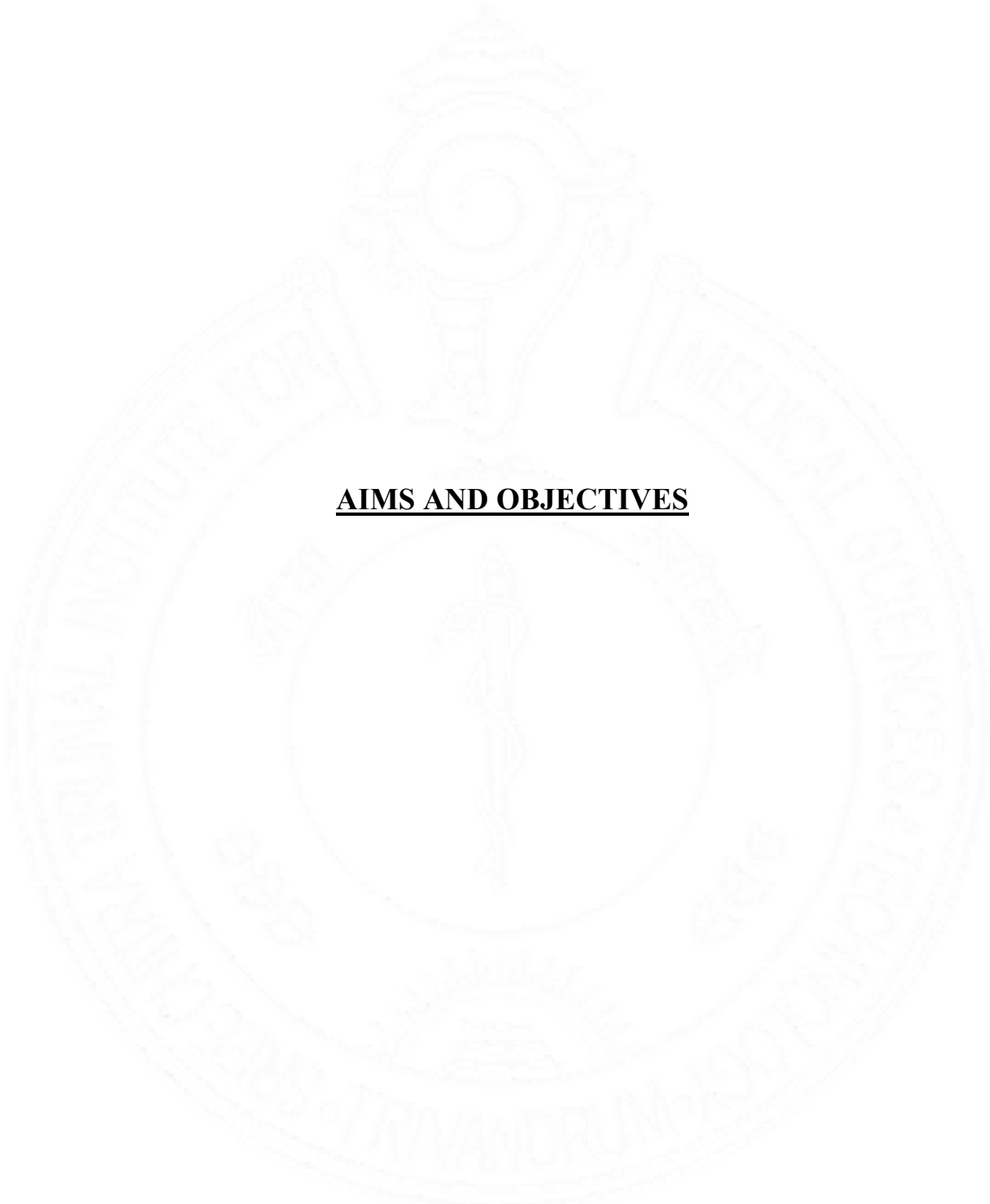


INTRODUCTION

Pituitary adenomas (PAs) most frequently extend beyond the sella into suprasellar, parasellar, and infrasellar regions. Parasellar extension into the cavernous sinus (CS) is seen in 10 to 40% of surgical cases as per multiple studies. [1](#) [2](#) [3](#) [4](#) [5](#)

PA with parasellar extension often attains large sizes yet the clinical signs of cavernous sinus invasion (CSI) occur late (5) as the intracavernous cranial nerves are located lateral to the intracavernous internal carotid artery (ICA). Cavernous sinus invasion is considered to be a marker for biologically aggressive neoplasms and increases the morbidity and mortality associated with surgical interventions (6), even if the tumors are histologically benign (7).

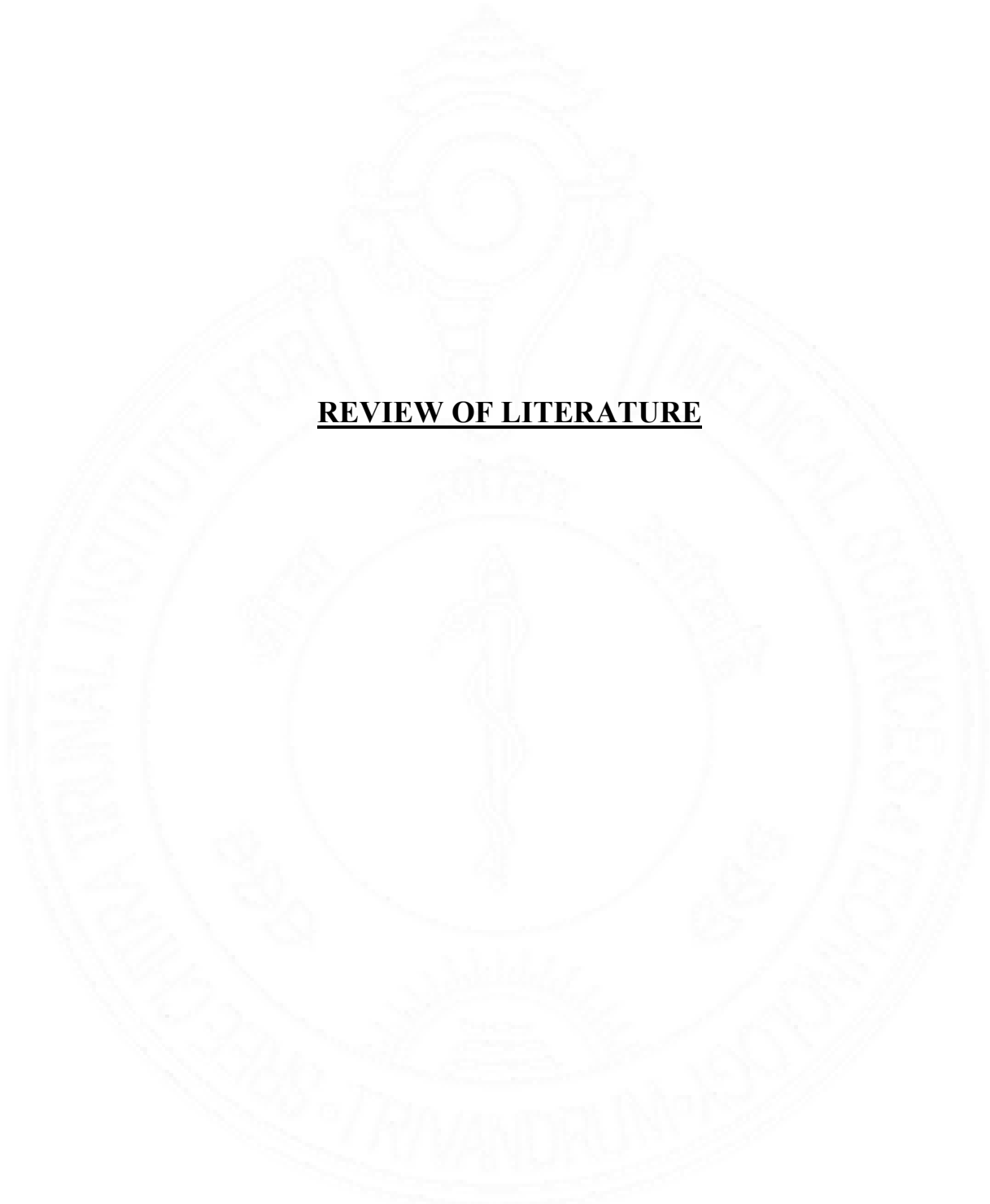
CSI by pituitary adenomas form a significant risk factor for incomplete surgical resection. Whether it is a true invasion suggesting an aggressive process or mere opportunistic intrusion into the weak medial wall of cavernous sinus. The management of intracavernous component of PA is controversial. Surgical resection of tumor in the CS risks complications, [6](#) [7](#) but these can be minimized by thorough understanding of the microsurgical anatomy of the CS and endoscopic techniques. [8](#) [9](#) [10](#) [11](#) Direct intraoperative observation serves as a more accurate method than radiology in assessment of the integrity of medial wall of CS.



AIMS AND OBJECTIVES

1. To analyse currently existing MRI based classification of CSI correlates with detection of cavernous sinus invasion during surgery
2. To re-evaluate the existing parasellar classifications using an endoscopic technique.





REVIEW OF LITERATURE

PITUITARY ADENOMA

Pituitary adenomas are tumors arising from the anterior pituitary. Most pituitary tumors are slow-growing and benign and are classified based on various parameters such as size or cell of origin. Pituitary adenoma can be micro/macroadenoma and giant tumors based on size. Microadenoma is a tumor less than 10 mm, while macroadenoma describes a tumor larger than 10mm. Giant pituitary tumors are bigger than 40 mm. There are functioning pituitary adenomas in which the cell type that composes them causes increased secretion of one or multiple hormones of the anterior pituitary. Alternatively, there are nonfunctioning adenomas that do not secrete hormones, but they can potentially compress the surrounding areas of the anterior pituitary leading to hormonal deficiencies. Patients with pituitary adenoma need to be evaluated by a multidisciplinary team that should include endocrinology, ophthalmology and neurosurgery.[\[1\]](#)[\[2\]](#)[\[3\]](#)

Pituitary adenomas are mostly found incidentally on imaging modalities obtained for other reasons. Given the insidious nature of the pituitary adenomas, smaller size, and incidental diagnosis, it is challenging to accurately estimate the prevalence of pituitary adenomas in the general population. The estimated prevalence of pituitary adenomas is extrapolated from autopsy and radiological

data. There is a wide range of prevalence among studies and the source of information.^[1] In a meta-analysis the pituitary adenomas frequency was 16.7% average; in autopsies 14.4% and in radiology tests 22.5%^[9] There are several population-based studies from different geographic areas spanned over many years to describe the epidemiology of the pituitary adenomas. The most popular study from Iceland showed a prevalence of 115 per 100,000 population.^{[1][10][2][11]}

The presentation of pituitary adenoma depends on tumor size and functional status.^{[1][2][11]}

Pituitary microadenoma is usually an incidental finding on MRI head. Patients are asymptomatic unless the tumor is hormonally active.

Pituitary macroadenoma presents with mass effects and potentially hormonal deficiency or hormonal excess.

Pituitary apoplexy is a sudden hemorrhage into pituitary adenoma. It is very rare. It presents with symptoms of a mass effect that includes sudden headaches and vision changes along with hormonal deficiency.

1. Symptoms from Mass Effect:

- **Visual impairment:** Visual impairment is reported in approximated 40% to 60% of patients. Suprasellar extension of the pituitary adenoma compresses the optic chiasm leading to visual field defects. Bitemporal defect is the most prevalent pattern, followed by homonymous defects. The involvement of the oculomotor nerve can lead to diplopia, while the fourth, fifth, and sixth cranial nerves may also be involved with invasive tumors.[\[12\]](#)[\[13\]](#)
- **Headache:** Headache is commonly reported in pituitary adenoma; however, it is a non-specific symptom.[\[13\]](#)
- **Hormonal deficiency:** One or more anterior pituitary hormonal deficiencies can be observed in patients with pituitary macroadenoma.

2. Functioning or secreting adenomas: The clinical presentation depends on the hormone secreted as described below:

- **Prolactin-secreting adenoma:** Elevated prolactin suppresses the gonadotrophin levels leading to infertility, decrease libido, and osteoporosis in both sexes. Females present with amenorrhea and galactorrhea while men present with erectile dysfunction and gynecomastia.

- **GH secreting adenoma (acromegaly):** Presentation includes headaches, vision changes, an increase in ring or shoe size, arthritis, carpal tunnel syndrome, and excessive sweating. Clinically patients have coarse facial features, frontal bossing, enlarged nose, prognathism, enlarged tongue, and skin tags. Other comorbidities like hypertension, cardiomyopathy, obstructive sleep apnea, and multiple colonic polyps may be present at the time of diagnosis.
- **ACTH-secreting adenoma (Cushing disease):** Presents with weight gain, muscle weakness, mood disorders, easy bruising, and multiple fractures. Clinical features include a round face, facial plethora, supra-clavicular fat, ecchymoses, and purple striae on the abdominal area and armpits.
- **TSH secreting adenoma:** Patients have symptoms of palpitations, arrhythmias, and weight loss. On exam, they may have tremors and a goiter.

Pathogenesis

The pathogenesis of pituitary adenoma remains unknown. Most of the pituitary adenomas are sporadic. In a study from Iceland with 410 pituitary adenomas, 43% were non-functioning adenomas, 40% prolactin-secreting adenomas, 11 % growth hormone (GH) secreting adenomas, and 6% Adrenocorticotrophic hormone (ACTH) secreting adenomas. Genetic mutation is rarely a feature of pituitary adenoma.[10] Familial cases of pituitary adenomas represent 5% of all pituitary tumors.[4] Mutation in the following genes has been found to play a role in the development of pituitary adenomas.

Multiple endocrine neoplasia type 1 (MEN1): MEN1 is a tumor suppressor gene. Loss of function mutation in this gene leads to tumor formation in the parathyroid, pancreatic, and pituitary glands.[5]

Multiple endocrine neoplasia type 4 (MEN4): MEN 4 has a mutation in the cyclin-dependent kinase inhibitor 1 B gene (CDKN1B) presenting with pituitary tumors, hyperparathyroidism, testicular, and cervical neuroendocrine tumors.[6]

Carney complex (CNC): In the Carney complex, there is a germline mutation of the tumor suppressor gene PRKAR1A leading to primary pigmented nodular

adrenocortical disease (PPNAD), testicular tumors, thyroid nodules, spotty skin hyperpigmentation, and acromegaly. [7]

Familial isolated pituitary adenomas (FIPA): Aryl hydrocarbon receptor-interacting protein (AIP) mutation is reported in adolescence or early adulthood in about 15% of all FIPA. These tumors are usually aggressive and they most commonly secrete growth hormone causing acromegaly. [8]

Molecular classification

The classification of tumours of the pituitary gland has recently been revised in the 2021 5th edition World Health Organization (WHO) Classification of Central Nervous

System Tumours (CNS5) and 2022 5th edition WHO Classification of Endocrine and Neuroendocrine Tumours (ENDO5). Adenohypophyseal tumors, which were recently renamed pituitary neuroendocrine tumors (PitNET), are mostly benign, but may present various behaviors: invasive, “aggressive” and malignant with metastases. They are classified into seven morphofunctional types and three lineages: lactotroph, somatotroph and thyrotroph (PIT1 lineage), corticotroph

(TPIT lineage) or gonadotroph (SF1 lineage), null cell or immunonegative tumor and plurihormonal tumors.

Morphological and Functional Classification in 2020

The 2017 WHO classification [1] recognized the relevance of lineage-restricted pituitary transcription factors (TFs) to classify tumors of adenohypophyseal cells and divided them into the three following lineages: PIT1 (pituitary specific transcription factor 1), TPIT (pituitary cell restricted factor), SF1 (splicing transcription factor 1). Lactotroph, somatotroph and thyrotroph belong to the PIT1 lineage, corticotroph to the TPIT lineage and gonadotroph to the SF1 lineage. Null cell and plurihormonal tumors are separate groups. Subtyping based on EM (electron microscopy) was abandoned because EM is not in routine use.

Lineage-Restricted Transcription Factors

The differentiation of normal pituitary cells during embryonic development depends on TFs. In brief, PIT1 drives the differentiation of somatotroph, lactotroph and thyrotroph cells and it is associated with ER (Estrogen receptor) and GATA2 (GATA transcription factor 2) for lactotroph and thyrotroph differentiation

respectively. Corticotroph differentiation depends on TPIT and NeuroD1 (neurogenic differentiation), and the gonadotroph lineage depends on SF1 and GATA2 [34,35,36,37]. A recent study suggested the use of GATA3 as complementary to SF1 in the diagnosis of gonadotroph tumor [38].

WHO 2017 Classification of Pituitary Adenomas, adapted from [1].

Adenoma Types		Immunophenotypes	Transcription Factors
Somatotroph Adenoma	Densely granulated adenoma	GH $\pm$ PRL $\pm$ α -su LMW CK: diffuse	Pit-1
	Sparsely granulated adenoma	GH $\pm$ PRL LMW CK: fibrous bodies	Pit-1
	Mammotroph adenoma	GH + PRL (in same cell) $\pm$ α -su	Pit-1, ER α
	Mixed Somatotroph-Lactotroph adenoma	GH + PRL (in different cells) $\pm$ α -su	Pit-1, ER α
Lactotroph Adenoma	Sparsely granulated adenoma	PRL	Pit-1, ER α
	Densely granulated adenoma	PRL	Pit-1, ER α
	Acidophilic stem cell adenoma	PRL, GH (focal and inconstant)	
Thyrotroph Adenoma		β TSH, α -su	Pit-1, GATA2
Corticotroph Adenoma	Densely granulated adenoma	ACTH, LMW CK: diffuse pattern	Tpit
	Sparsely granulated adenoma	ACTH, LMW CK: diffuse pattern	Tpit
	Crooke's cell adenoma	ACTH, LMW CK: ring-like pattern	Tpit
Gonadotroph adenoma	Sparsely granulated	β FSH, β LH, α -su (various combinations)	SF-1, GATA2, ER α (variable)
Null cell adenoma		None	None
Plurihormonal adenomas Pit-1 positive plurihormonal adenoma (previously termed Silent subtype 3 adenoma)		GH, PRL, β TSH $\pm$ α -su	Pit-1
Adenomas with unusual immunohistochemical combinations		Various combinations	
Double adenomas	Distinct adenomas	Usually PRL and ACTH adenomas	Pit-1 and Tpit, respectively

Radiological classification

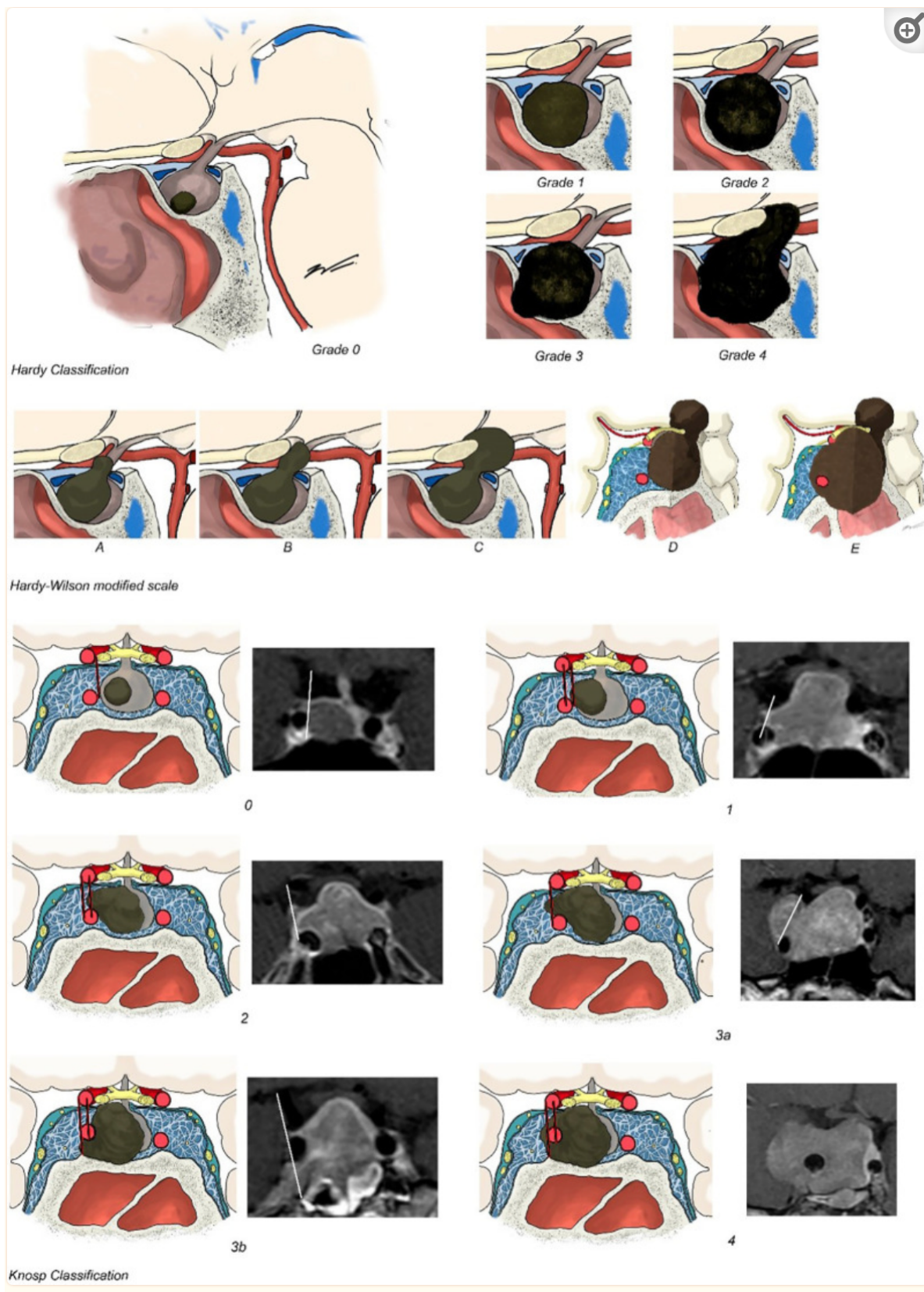
The earliest universally accepted, radiographic and operative classification of local invasion was proposed by Hardy et al. in 1976 (5) and later modified by Wilson in 1979 to distinguish between different grades of extrasellar extension (6). In 1993,

Knosp et al. described the classical radiological classification of cavernous sinus invasion based on the relations of the PAs with the line between the supraclinoid internal carotid artery (ICA) and intra-cavernous ICA on coronal magnetic resonance imaging (MRI) ([7](#)). Several studies have found that the Knosp grade is a good predictor of surgical outcomes ([4](#), [8](#), [9](#)). Later studies have found that the revised-Knosp classification ([3](#)), which includes the differentiation between superior or inferior cavernous sinus compartment invasion in grades 3A and 3B, provides a better prediction of gross total resection and endocrine remission in functioning PAs ([10](#)).

The Hardy–Wilson classification considered the degree of sellar destruction (grade) and extrasellar extension (stage) ([14](#)). Sellar destruction was divided into the following: Grade 0 when the enclosed adenoma is described as a tumor that remains within the anatomical confines of the osteoaponeural sheath of the sella turcica; Grade I: the sella turcica is within normal limits in size or focally expanded and the tumor is <10 mm; Grade II: tumor $\geq$ 10 mm and the sella turcica is enlarged but the floor remains intact; Grade III: a local erosion or destruction of the floor; Grade IV when the entire floor of the sella is diffusely eroded or destroyed, giving a characteristic “phantom sella” with all the boundaries barely

visible. Extrasellar extension according to the Hardy–Wilson modified scale is divided into stage 0, with no suprasellar extension, A–C for progressive suprasellar extension (A: occupying cistern, B: recess of third ventricle obliterated, and C: third ventricle grossly displaced), and D–E grading parasellar extension (D: intracranial extension and E: cavernous sinus extension) ([Figure 2](#)).

Cavernous sinus invasion was evaluated using the Knosp–Steiner classification based on coronal T1-weighted contrasted imaging ([15](#)): Knosp 0 when PA is medial to medial tangent; Knosp 1 if PA extends to the space between the medial tangent and the intercarotid line; Knosp 2 when PA extends to the space between the intercarotid line and the lateral tangent; Knosp 3 if PA extends lateral to the lateral tangent; and Knosp 4 with a complete encasement of intracavernous ICA. Knosp score 3–4 were considered as invasive PA. Moreover, radiological reports were reviewed to include the revised-Knosp classification ([3](#), [5](#)). The revised-Knosp classification includes 2 subtypes of grade 3: Knosp 3A when PA is above the intracavernous ICA into the superior cavernous sinus compartment and Knosp 3B when PA is below the intracavernous ICA into the inferior cavernous sinus compartment ([Figures 2](#) and [3](#)).



Csi

The encroachment of cavernous sinus (CS) by pituitary adenomas, often termed CS invasion (CSI), is the most common and significant risk factor for their incomplete surgical resection.^{1, 2, 3, 4} Whether it is true invasion suggesting an aggressive process or mere opportunistic intrusion into the weak wall of the CS, the determination of CSI has been problematic. The varied radiologic criteria described are not universally accepted and may not reliably determine invasion. Direct observation is hence considered more accurate than radiology in the absence of histologic assessment of the integrity of the medial wall of CS, which is often not feasible.^{5, 6, 7} Nevertheless, direct observation too can be inaccurate depending on who is observing, with what degree of exposure, and potentially misleading because tumor has to be removed to evaluate the integrity of the medial CS wall.^{8, 9, 10, 11, 12, 13} These limitations have resulted in variable and inconsistent reports on the impact of CSI on pituitary adenoma surgery.^{14, 15, 16, 17, 18, 19}

Deliberate resection of the medial wall of the cavernous sinus has long been considered morbid and unattainable, which has contributed to its controversy in pituitary surgery^{12,13}. Oldfield first recognized the medial wall of the cavernous

sinus as a frequent nidus for recurrence in Cushing's disease and advocated for its removal^{4,19,20}. Recent laboratory investigations have better elucidated the microsurgical anatomy of the medial wall of the cavernous sinus. By defining the parasellar ligaments that tether the wall to cavernous sinus structures, this allowed for the development of an innovative surgical technique for its safe removal^{12,13}. The use of histological analysis of the medial wall itself has further advanced the visualization of microscopic invasion^{13,21,22}, a more precise way of assessing cavernous sinus invasion compared to sellar floor dural sampling^{4,5,8,20,23} or visualization of clival recess invasion as previously performed by other groups^{8,24}. Medial wall histological analysis allows for improved validation and understanding of the limitations of current preoperative radiographic classification systems that suggest invasion while identifying adenoma subtypes with a predilection for cavernous sinus invasion.

Management of Pituitary Adenomas

The management of pituitary adenomas requires an endocrinologist and a neurosurgeon to work closely together and develop an "individualized patient-centric" approach.^{[1][2][11][15][16][12][17][14]}

Treatment of Non-Functioning Adenomas

Transsphenoidal resection is recommended in patients with macroadenomas and the following scenarios:

- Visual field deficit due to tumor
- Other visual abnormalities as ophthalmoplegia
- Compression of the optic nerves or chiasm on imaging
- Pituitary apoplexy with visual disturbance
- Loss of endocrine function
- Significant growth of pituitary tumor over time

After surgery there is usually an improvement in visual symptoms and hormonal dysfunction in most patients. Radiotherapy is a consideration in patients with persistent residual or recurrent tumor.

In nonfunctional adenomas that do not require surgical management, annual follow-up with endocrinology is important to assess for tumoral growth and development of hypopituitarism. MRI of head is obtained annually for three years and if stable, thereafter less frequently.

Treatment of Individual Functioning Tumors

- **Prolactin-Secreting Adenoma:** The goal of treatment is to restore gonadal function and decrease tumor size. Observation with periodic monitoring of prolactin levels can be an option in patients who are asymptomatic with microadenoma.

Medical Therapy

Dopamine agonists (DA) are the first-line treatment for prolactin-secreting tumors. The currently available DAs are cabergoline and bromocriptine. Cabergoline is more than 90% effective in normalizing prolactin levels and decreasing tumor size. The adverse effects of DA are dizziness due to postural hypotension, valvular heart abnormalities, and the development of compulsive behavior or mood changes. DA could be discontinued after two years of treatment if the MRI of head did not show a visible tumor. Monitoring serum prolactin levels annually is needed in these patients as there is some risk of recurrence or growth after stopping DA.

Surgery

Transsphenoidal surgery is often reserved for prolactin-secreting tumors which are resistant to medical treatment, patients who develop adverse effects to dopamine

agonists and, in patients desiring pregnancy with tumor size of more than one centimeter.

Radiation Therapy

Radiotherapy is seldom used in cases of aggressive prolactinomas, where frequent surgeries and medical therapy have failed to control the size of the adenoma.

- **GH Secreting adenoma:** The goal is to decrease growth hormone levels to less than 1ug/L and get IGF-1 levels to the normal age-adjusted range.

Surgery: Trans-sphenoidal surgery is the first-line treatment for GH-secreting tumors. In the hands of an experienced surgeon, normalization of IGF-1 is achieved in 80% to 90% of patients with microadenomas and 40% to 60% of patients with macroadenomas.

Medical therapy: Medical treatment is considered in patients with persistently elevated IGF-1 and GH levels at three months after surgery or in non-surgical candidates with invasive tumors. Somatostatin analogs (SSA) are the first-line treatment for acromegaly. Current available SSAs are octreotide, lanreotide, and pasireotide. The adverse effects of SSA include gallbladder sludge and stones, abdominal cramps, flatulence, diarrhea, and alopecia. Pasireotide can lead to

hyperglycemia in 50 to 70% of patients. DA, like cabergoline, is also used for mildly elevated IGF-1 level post-surgery or as an adjunct therapy with SSA. If the GH remains elevated, pegvisomant, a GH receptor blocker, can be used in combination with SSA or alone for the treatment of acromegaly.

Radiotherapy: Radiation treatment may be used as an adjunct in patients with elevated IGF-1 levels after surgery, but it will take several years to be effective.

- **ACTH secreting adenoma:** The goal of treatment is to decrease cortisol levels rapidly and to reduce the associated complications and mortality.

Surgery: Trans-sphenoidal surgery is the first-line treatment for Cushing's disease. The cure rate is 70% to 90 % in the hands of an expert surgeon with initial and repeated surgeries.

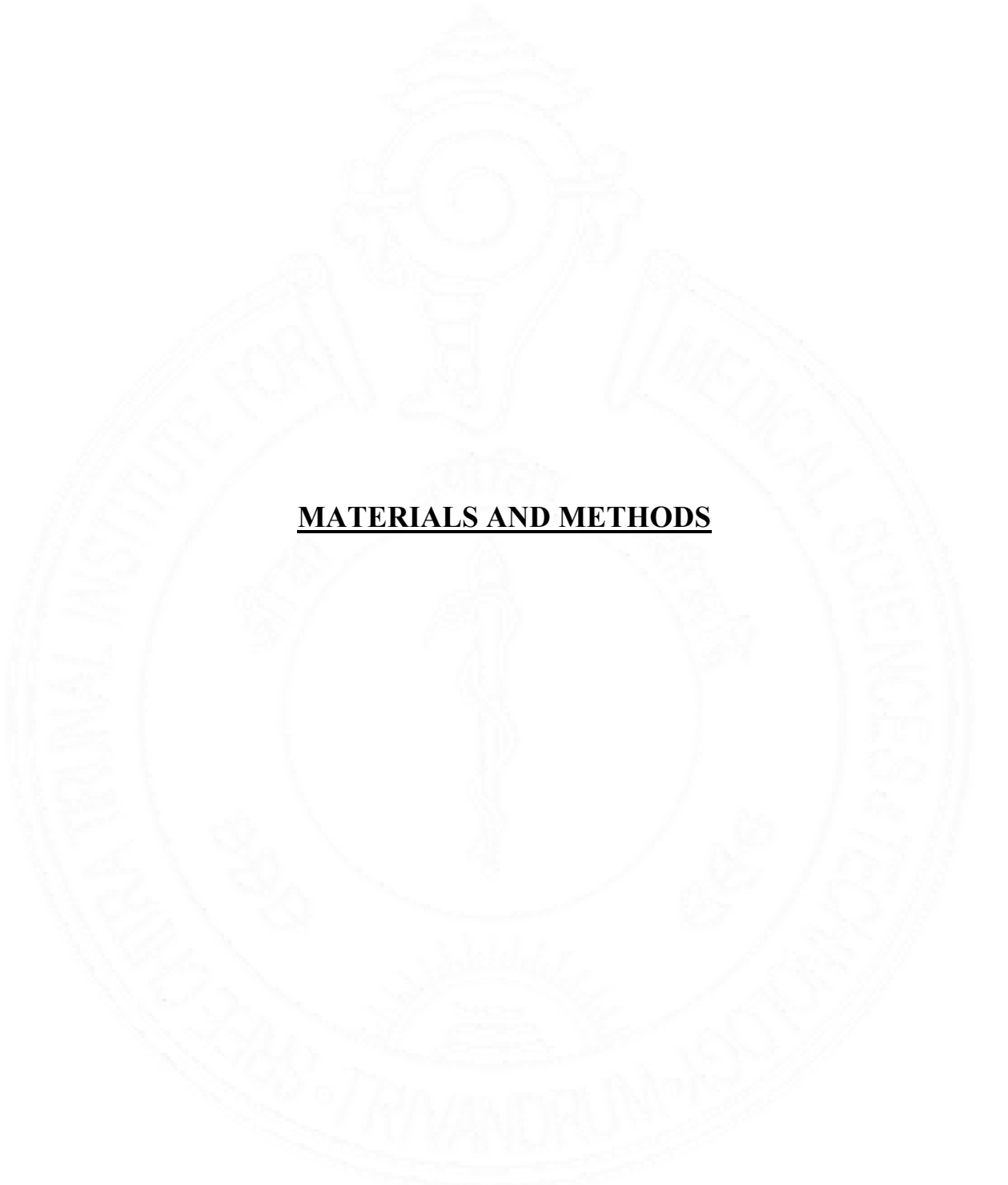
Medical therapy: DA (cabergoline) and SSA (pasireotide, pasireotide LAR) are the drugs directed at the pituitary to decrease ACTH secretion. Ketoconazole, metyrapone, mitotane, and etomidate also decrease adrenal cortisol production. Ketoconazole can lead to liver toxicity and prolongation of the QT interval. Metyrapone is 50 to 60% effective in reducing the cortisol level. Mitotane is an adrenolytic drug, mostly used in patients with adrenocortical cancer. Etomidate is

given intravenously in critically ill patients with severe hypercortisolemia as a bridge to work on other treatment interventions. The glucocorticoid receptor blocker, Mifepristone, can be used in selected patients with hypercortisolemia and diabetes.

Bilateral adrenalectomy can lead to an immediate cure of hypercortisolemia with resultant adrenal insufficiency requiring lifelong treatment. Nelson syndrome, which is radiological pituitary tumor enlargement, can occur in 50 % of patients after adrenalectomy.

Radiotherapy: Radiation treatment serves as an adjunct after surgery and medical therapy.

- **TSH secreting adenoma:** Trans-sphenoidal surgery is the initial preferred treatment option leading to a cure in 50% to 90% of patients. It is crucial to control hyperthyroidism before surgery to avoid thyroid storm. Presurgical euthyroidism is achieved by using anti-thyroidal medical therapy like methimazole or SSA. Patients who are not cured by surgery can be treated with SSA alone to decrease TSH levels and tumor size, or in combination with radiation treatment.



MATERIALS AND METHODS

Study design, patient selection and randomization

A single-center, prospective-retrospective study was conducted at our institute between 2015 and 2023 on patients who underwent endoscopic transnasal transsphenoidal surgery for Pituitary adenomas.

Inclusion Criteria: All patients diagnosed with pituitary adenomas requiring endoscopic transnasal transsphenoid approach for management.

Exclusion Criteria: Redo surgeries.

Pre-surgical work up

All the patients underwent a standard presurgical work up for pituitary adenomas as per institutional protocols and established standards of care. Clinical and radiological assessment of patients were done pre-operatively, followed by surgical resection of tumors and assessment of CSI. CT Brain done routinely for patients on admission were be documented.

Pathological examination

Four-micrometer-thick histologic sections were generated from 10% formalin fixed, paraffin-embedded tissue and stained with hematoxylin and eosin (H&E) by

a specialised neuropathologist (DN). WHO classification of PitNets (2017 and 2021 revision) were followed.

Post-operative assessment

Clinical assessment of patient were done on Post-operative day 1 and 2 weeks later to look for any neurological deficit. Radiological assessment were based on routine post operative CT scan obtained on first post operative day.

STATISTICAL ANALYSIS

For nominal and ordinal independent variables, we performed the cross-tabulation, chi-squared tests, and Fisher's exact tests to analyse categorical variables. In the case of quantitative variables, we performed the t-test and ANOVA tests. For calculation of effect sizes, the odds ratio (OR) was used for categorical data. All tests were two-tailed. Statistical analysis was done using SPSS software version 21.0

RESULTS

Between January 2015 and October 2023, a total of 312 patients underwent primary surgery for PA in our institute.

Variables	
Total number of cases	312
Age (in years)	45.5 ± 12.5 years
Intra-operative CSI	70 (22.43%)
Gender	
Male	26 (37.14%)
Female	44 (62.85%)
Age	
Pediatric	01
Adult	69

Radiological CSI (Knosp grade $\geq 3a$) 48 (68.57%)

Clinical characteristics:

The mean age of the study group was 45.5 years (SD 12.5 years). Intra-operative CSI was noted in 70 patients (22.43%) which included 26 males (37.14%) and 44 females (62.85%). The study group consisted of 1 pediatric and 69 adult patients.

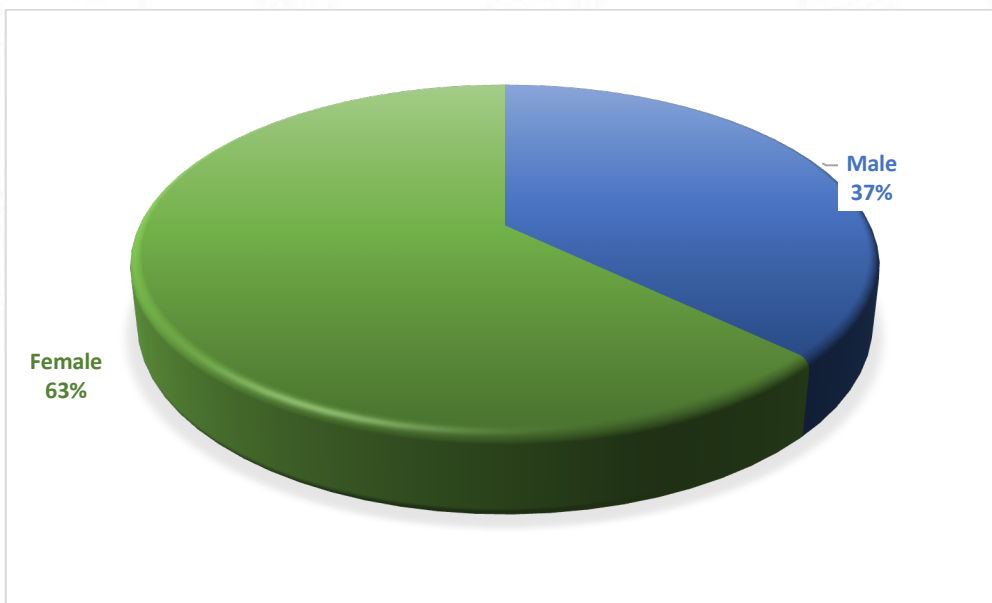
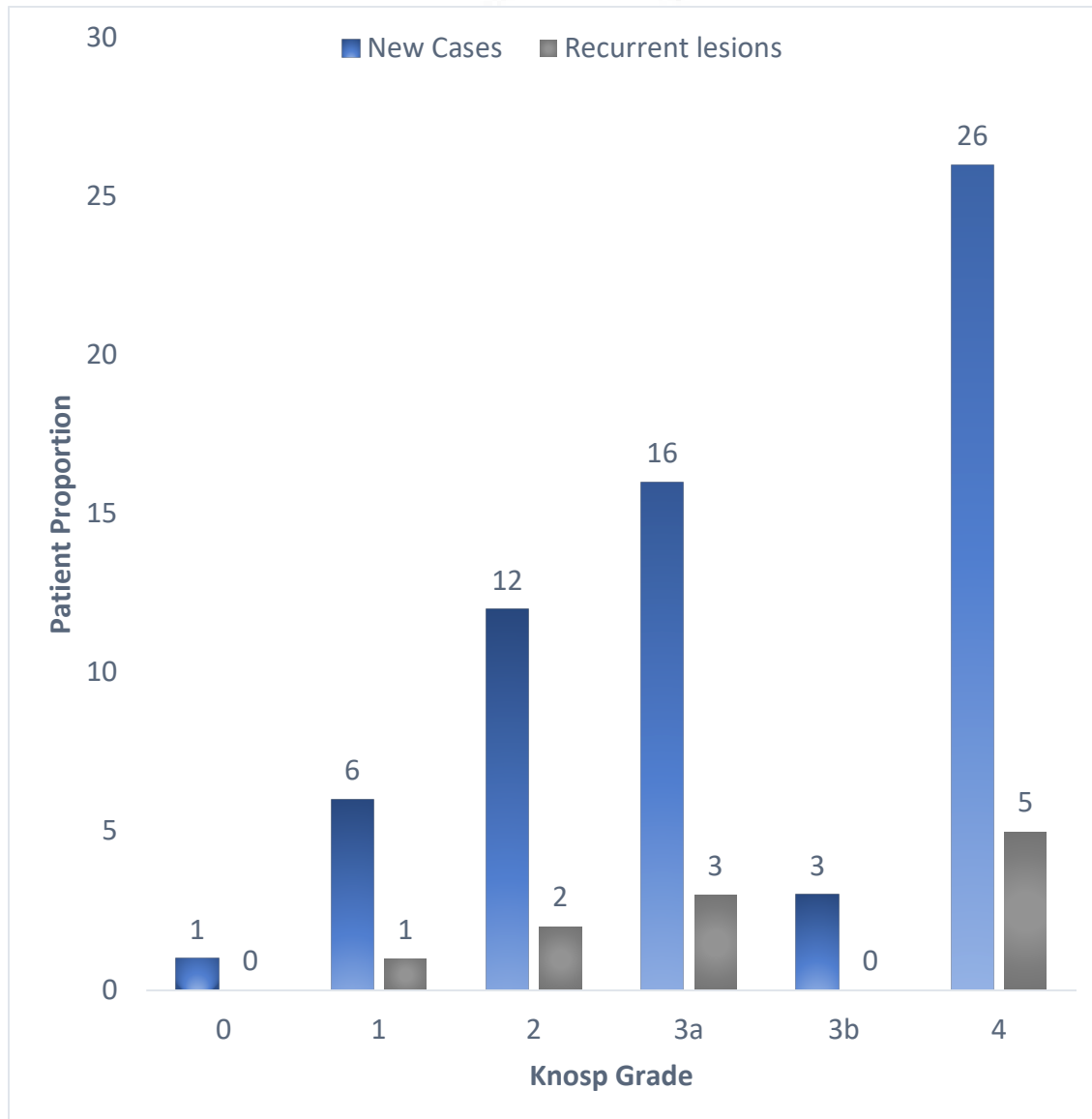
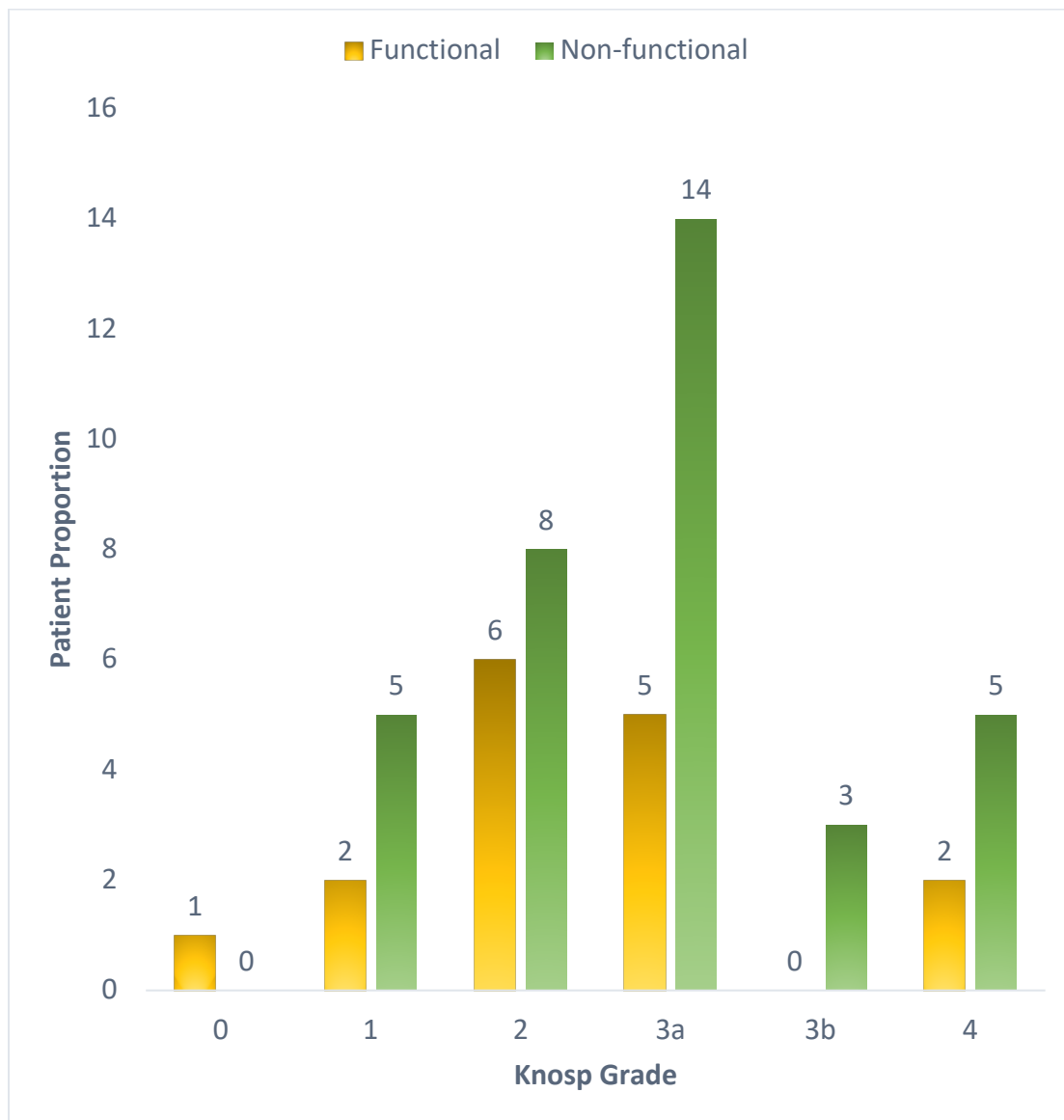


Figure 3. Gender distribution of study patients.

Radiological CSI (Knosp grade $\geq 3a$ was noted in 48 of the 70 patients (68.75%).

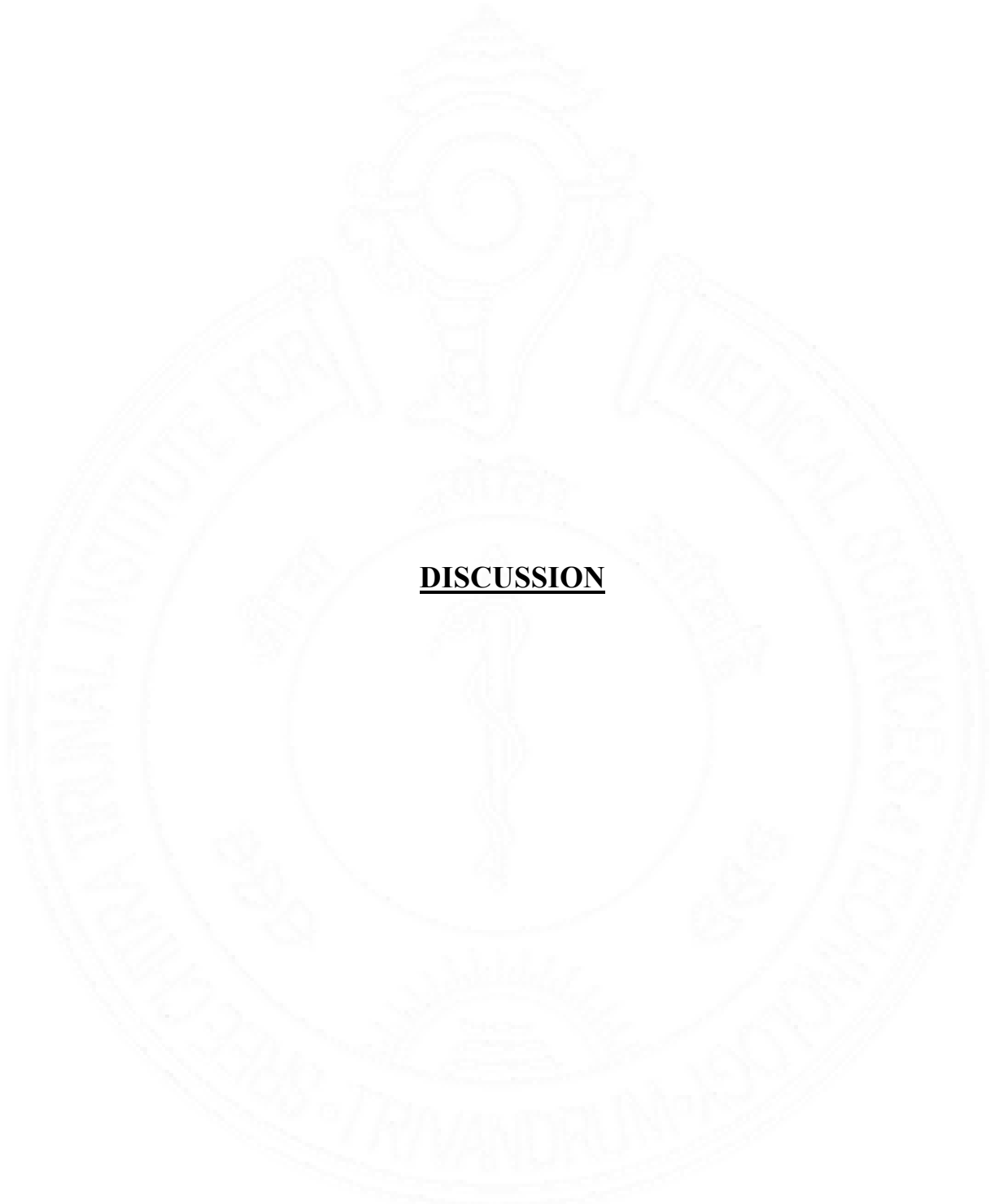




Radiological interpretation of CSI was less accurate in new cases (n=59) compared to recurrent (n=11) lesions (68.57% vs. 72.7%, p=1.0) whereas, interpretation in

non-functional PAs (n=54) were significant compared to functional (n=16) PAs (76% vs. 43.75%, $p < 0.0291$).

	rCSI	No rCSI	Total	p-value
New cases	40	19	59 (67.8%)	1.00
Recurrent lesions	8	3	11 (72.7%)	
			70	
Functional	7	9	16 (43.75%)	< 0.029
Non-functional	41	13	54 (76%)	
			70	



DISCUSSION

The consequences of cavernous sinus invasion by pituitary adenoma are clinically important because they render the surgical procedure more difficult and less efficient. Invasion increases the frequency of intraoperative injury to the intracavernous ICA and of postoperative cerebrospinal fluid leakage. Dural wall invasion usually implies partial surgical removal of the tumor (10) and requires additional therapy (ie, conventional radiation therapy, radiosurgery, or suppressive drugs). Because cavernous sinus invasion clearly influences the management and prognosis of pituitary adenoma (6), its preoperative diagnosis has to be as precise as possible.

The anatomic location of the pituitary gland determines its ability to expand laterally toward the cavernous spaces. Because there are no lateral bone boundaries to the pituitary fossa, the expansions develop mainly in these lateral directions, and 6%–10% of pituitary adenomas involve the cavernous sinus (1,2). The pituitary gland is contained in a dural bag attached to the inferior aspect of the diaphragm of sella and surrounded by venous spaces that correspond laterally to the cavernous sinuses (11). The so-called medial wall of the cavernous sinus is the lateral part of this thin dural bag. It forms a convex lateral margin along the pituitary fossa on a coronal or transverse MR section and allows lateral physiologic ex-

pansions of the pituitary gland in about 29% of cases (11,12). Invasive disease has to be distinguished from lateral expansion without invasion. In the latter case, one can imagine the growing tumor forming or extending a lateral expansion of the dural bag around the intracavernous ICA similar to the phenomenon that occurs when an inflated balloon is compressed by a rigid tube. As long as the dural bag remains intact, no invasion of the cavernous sinus occurs. It only occurs when a defect appears on the bag.

The standard-of-reference criterion for this study was the intraoperative report of cavernous sinus invasion. Even this criterion may be criticized because it depends on the intraoperative findings of the neurosurgeon—that is, direct visualization of and/or contact with the intracavernous ICA, and the invasion or lack of invasion cannot always be reliably determined, even surgically. Nevertheless, this is the least imprecise criterion that can be applied to living subjects.

The preoperative radiologic diagnosis of invasion is of course more difficult and based on CT and MR imaging findings. MR imaging was proved to be superior to CT in depicting the normal and abnormal pituitary gland and sellar region (8,13). At CT and MR imaging, the medial dural wall cannot be identified. MR imaging is superior to CT in enabling the identification of the intracavernous ICAs and

more clearly depicts the lateral dural wall (8). Analysis of the lateral venous spaces may be improved by using dynamic CT scanning (14).

During MR imaging, the absence of invasion can be assumed if a normal pituitary gland is present between the tumor and the intracavernous ICA or if a venous compartment is visible between the tumor and the intracavernous ICA (8,9).

On the other hand, total encasement of the intracavernous ICA is a very specific sign, but it is not very sensitive (8).

Preoperative assessment of invasion of the cavernous sinus with MR imaging remains difficult unless the pituitary gland or medial venous compartment is visible or there is circumferential encasement of the intracavernous ICA.

Alternative criteria have to be defined by using the limits of the cavernous sinus, its venous contents, and the intracavernous ICA.

Cavernous Sinus Limits

Depiction of the medial wall could have helped to confirm or exclude cavernous sinus invasion, but this thin structure was not seen at MR imaging in our study or

in previous reports (8,9), and it cannot be used for the MR imaging–based diagnosis of invasion.

The enormous variations in reported prevalence of CSI based on direct intraoperative observation (9%^{2,17}–30%¹⁹) compared with radiographic assessment (30%²⁸–63%²⁹) in pituitary adenomas show the ambiguity in defining CSI. Our meta-analysis noted a significantly higher prevalence of CSI radiographically (43%) than the intraoperative findings (18%) suggest.

Several radiologic criteria have been described in the literature to predict the intraoperative evidence of CSI. Although KS grades were noted to have a stepwise incremental risk of CSI,^{18,19,25} other investigators observed defects in the medial wall of CS,⁴⁰ venous compartment obliteration (CSVCO, ILVCO),⁹ APCE,⁴¹ and PEICA^{9,13,40,41} to be more valuable, albeit with no systematic comparative evaluation. Even with respect to PEICA, although Viera et al.¹³ noted 30% encasement as the optimal cutoff, other studies^{9,40} observed 67% as the best criteria.

KS grades have been used to define CSI in different ways. Whereas some noted KS 2e4^{14,29,30} to denote CSI, many others used KS 3e4.³¹⁻³⁵ We noted KS 3e4 to be better than KS 2e4 both in relation to operative CSI as well as in relation to the feasibility of GTR. Considering the importance of obliteration of inferior venous compartments (CSVCO and ILVCO),⁹ future studies need to incorporate further categorization of all KS grades into supracarotid and infracarotid extensions similar to 3A/3B categories proposed by Micko et al.¹⁸

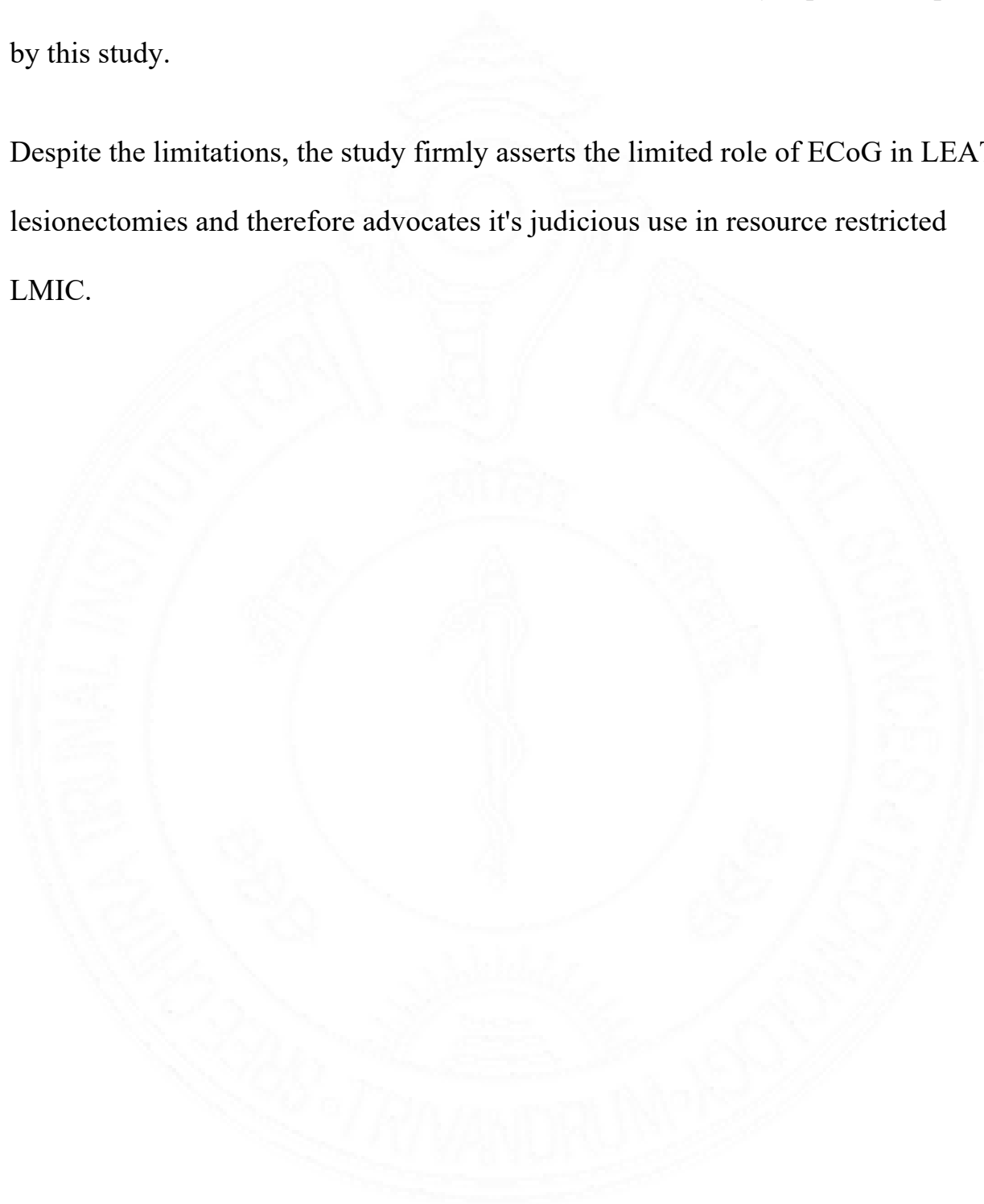
In the absence of a gold standard for defining CSI, intraoperative CSI should be compared across series based on objective grades of Knosp. Although, our data goes in accordance with worldwide reports for direct intraoperative observation (9%-30%), only about two third patients with intraoperative CSI had radiological evidence of the same.

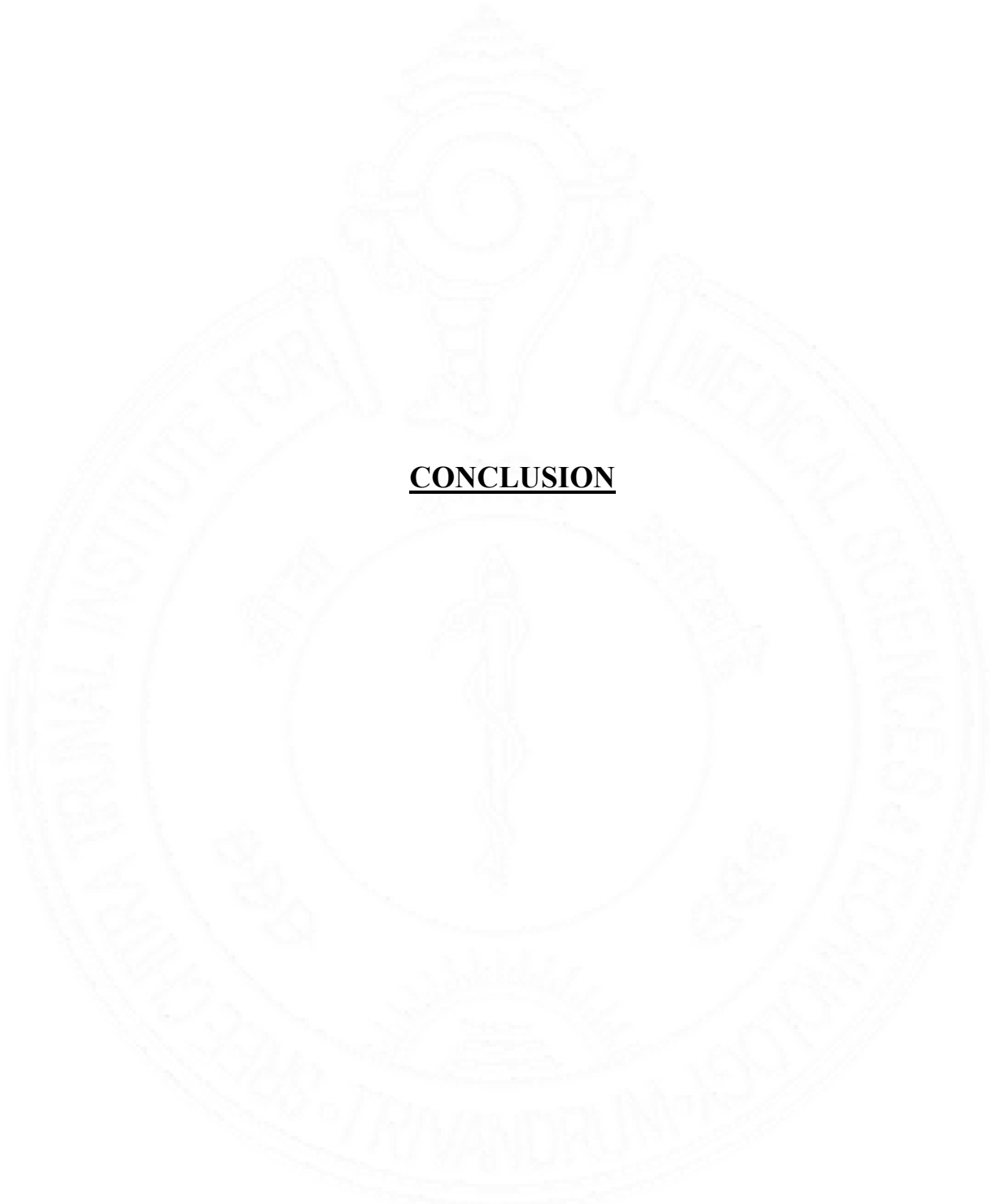
Study Limitations

This is a single-center series and thereby limits its generalizability. A longer duration of follow up would have helped to assess late failures. A correlation of pre-resection ECoG patterns with seizure outcome benefits could be of more value. Impact of ECoG recordings on long term prognostication, cost of care, resource,

time utilisation and withdrawal of anticonvulsants are the many aspects unexplored by this study.

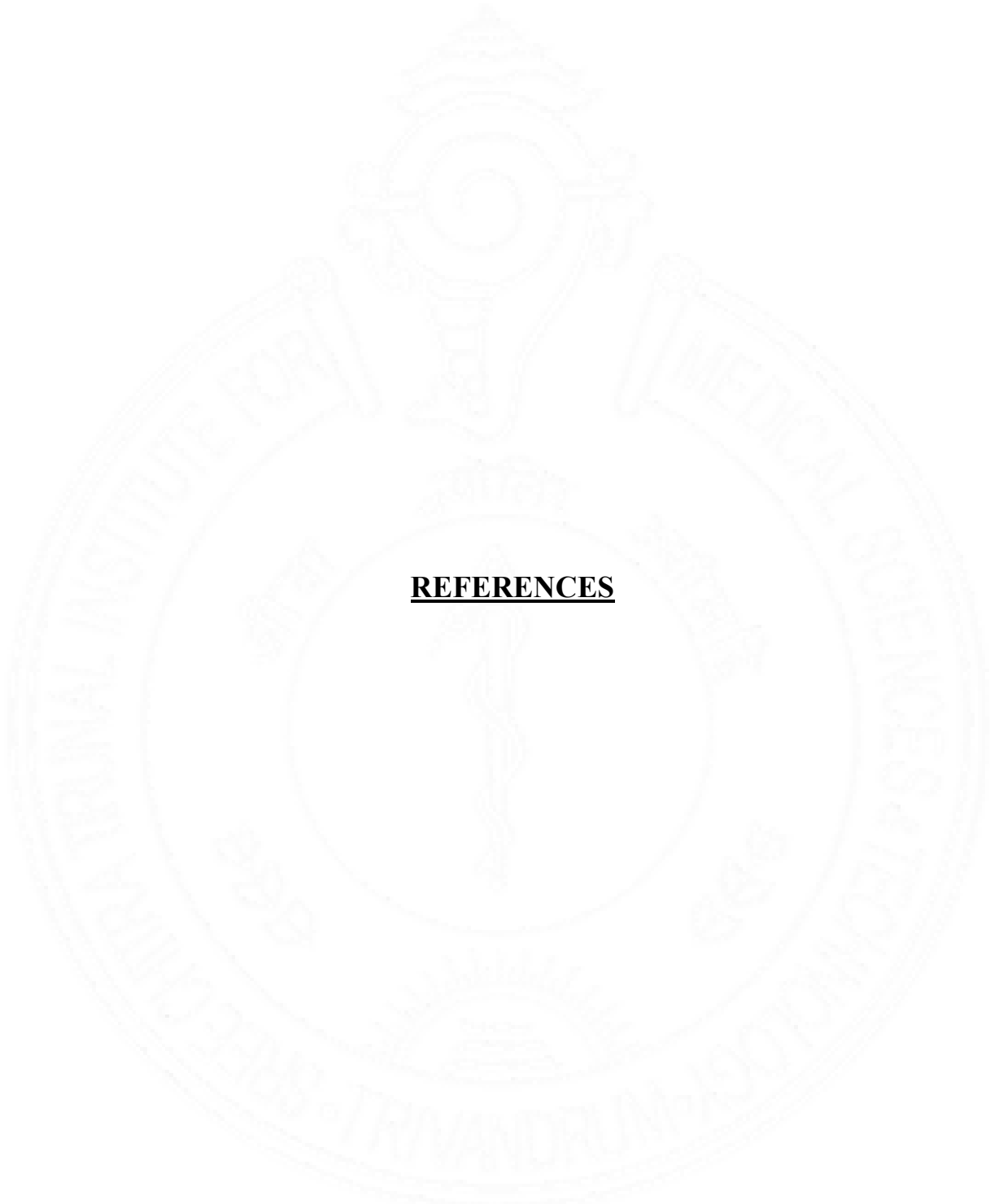
Despite the limitations, the study firmly asserts the limited role of ECoG in LEATs lesionectomies and therefore advocates it's judicious use in resource restricted LMIC.





CONCLUSION

CSI being an important determining factor in extent of resection in endoscopic PA surgeries carries the burden of radiological diagnostic ambiguity. Knosp grading is considered as an excellent tool for prognosticating surgical cure. Although, our data goes in accordance with worldwide reports for direct intraoperative observation (9%-30%), only about two third patients with intraoperative CSI had radiological evidence of the same.



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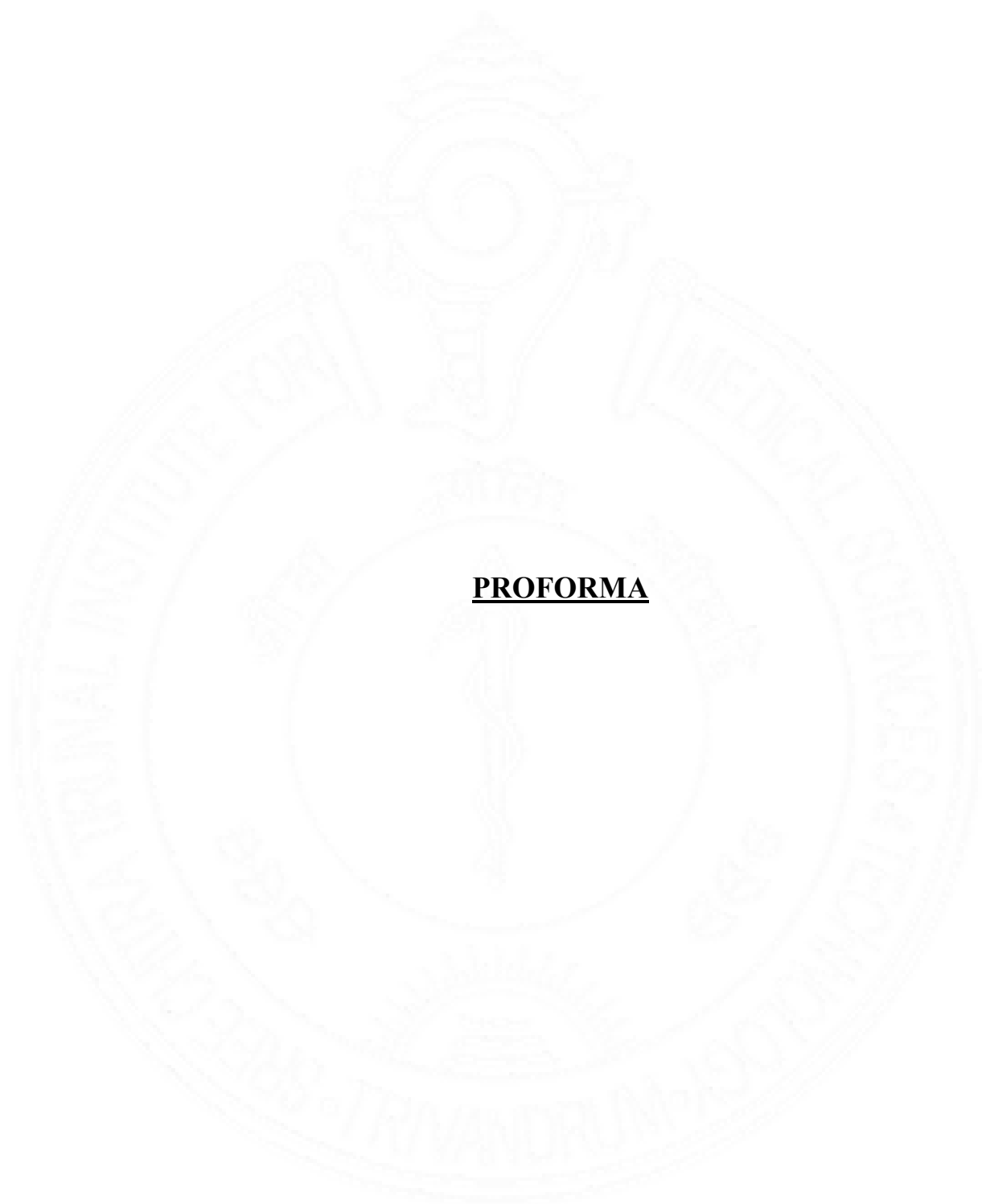
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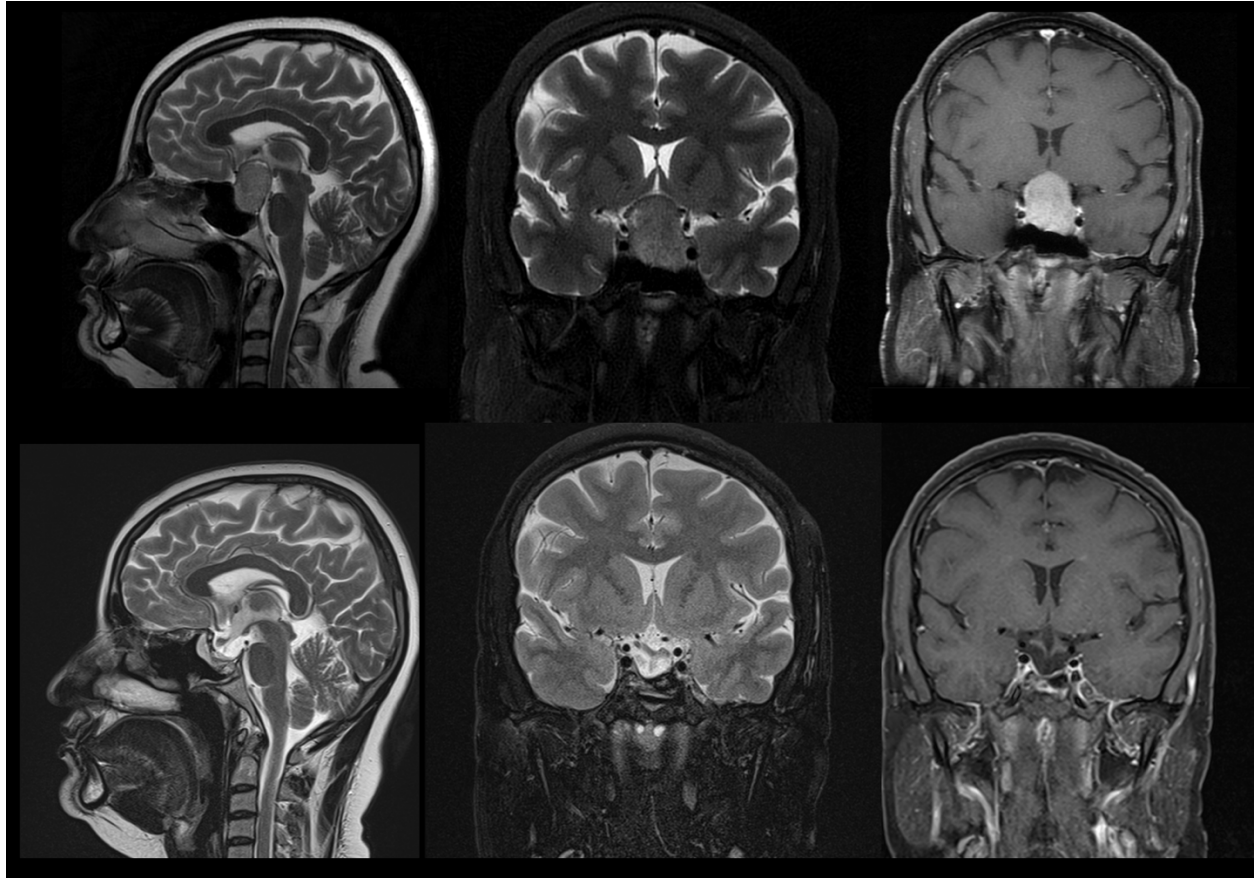
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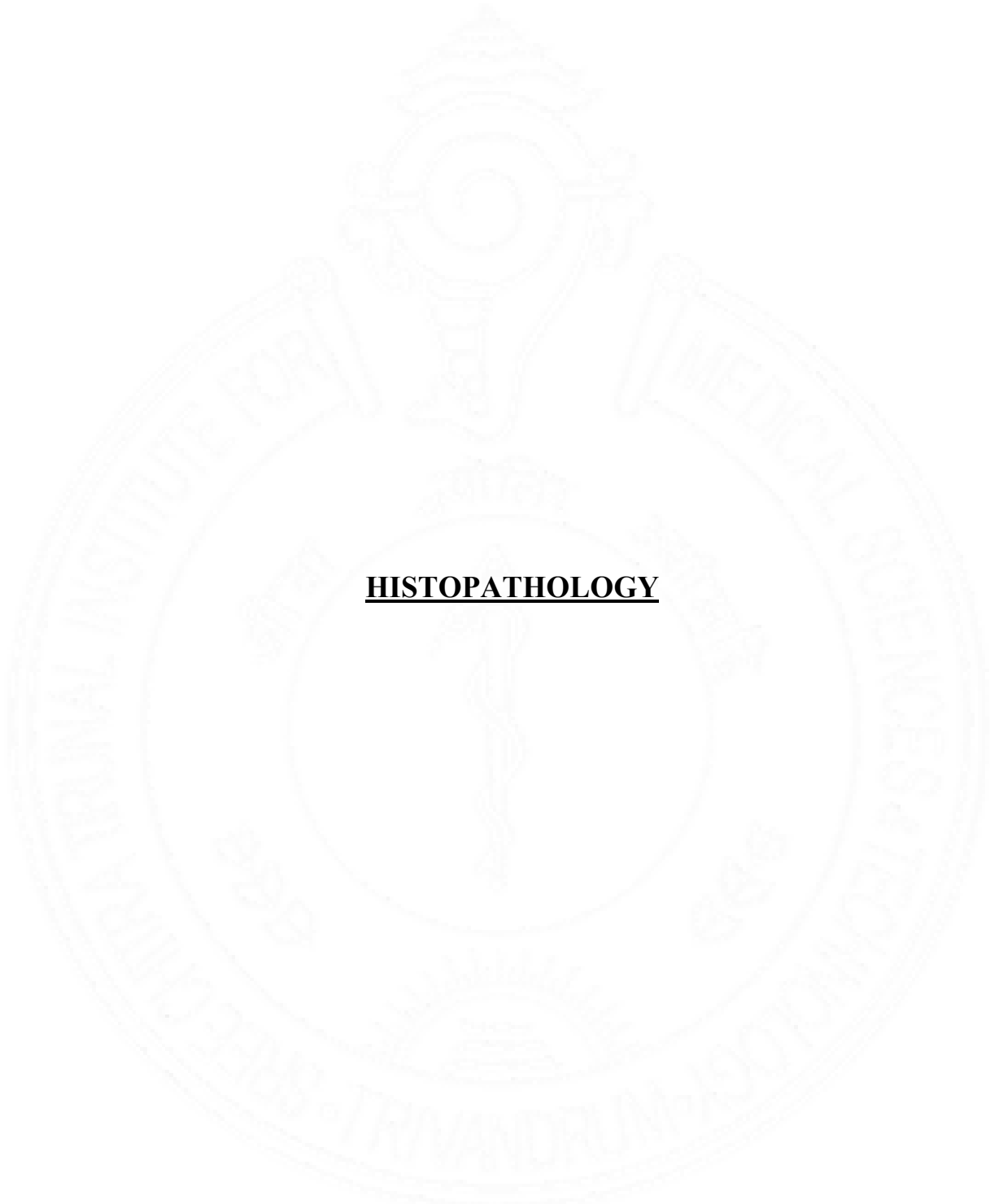
ANNEXURES



PROFORMA

CASE ILLUSTRATION





HISTOPATHOLOGY

