TREATMENT MODALITIES AND OUTCOMES OF PATIENTS WITH PITUITARY ADENOMA AT INKHOSI ALBERT LUTHULI CENTRAL HOSPITAL AT KWAZULU NATAL PROVINCE SOUTH AFRICA

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By

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A dissertation submitted in partial fulfilment of the requirements for Degree of Master of Science in Neurosurgery of Muhimbili University of Health and Allied Sciences.

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CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by Muhimbili University of Health And Allied Sciences a dissertation entitled ***Treatment Modalities and Outcomes of patients with Pituitary adenoma at Inkhosi Albert Luthuli Central Hospital in KZN South Africa,*** in (Partial) fulfilment of the requirement for the degree of Master of Science (Neurosurgery) of Muhimbili University of Health and Allied Sciences.

_____

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Date _____

DECLARATION AND COPYRIGHT

I , **Mugisha Clement Mazoko**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for similar or other degree award.

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DEDICATION

This work is dedicated to my parents Mr Clement Byakubakwo Mazoko and Mrs Leokadia Mazoko because of their good foundation to my success. May God Continue blessing you and grant you long life.

Lastly I dedicate this work to my beloved Wife Dr Grace Elias Magembe and my children Kemilembe Gabriella Mugisha and Kamugisha Gabriel Mugisha for their love and support.

ABSTRACT

Introduction: Pituitary tumours are common, estimated to constitute about 10 to 15 % of brain tumours. They have been studied extensively in developed world than developing and underdeveloped countries. Little is known in KwaZulu Natal province on what are outcomes of different treatment modalities of pituitary adenomas.

Objective: The study objective was to assess the treatment modalities and their outcome in patients presented with pituitary adenoma.

Materials and Methods: A descriptive cross-sectional retrospective study on patients who presented with pituitary adenomas at IALCH at Durban, KZN province in South Africa from January 2007 to December 2012. Patients were treated, medically, surgically and adjuvant medical and radiotherapy done. Treatment outcomes were assessed versus treatment modalities. Outcomes were considered as improved or not improved in patient preoperative symptoms, residual or no residual tumour. Complications of each treatment modality were assessed. Outcomes were computed and association were determined using Chi- square test and p-values.

Results: Out of 42 patients reviewed, 67.5% were female and 33% were males with a male to female ratio of 1:2. Fifty percent of patient had age above 40 years, mean age was 43 years ,with a range of 19 to 76years, median of 40 years (p-value <0.15). The main clinical presentations were, 48.4% of patient presented with symptoms related to visual disturbances, and 30.6% had headache. Laboratory results were reviewed , Out of 42 patients 6 had prolactinoma,8 had GH secreting tumours, 2 had ACTH secreting tumours. In those prolactinoma patients 66.6% had serum prolactin levels 5000 to 1000001ng/ml, when bromocriptine or carbergoline instituted and patients were followed up for 3 to 6months.It was found that they had both clinical ,visual, biochemical and radiological improvement and this was statistical significance (p-value <0.04).

Eight patients had GH secreting tumours , GH and IGF-1 levels compared preoperative and post operatives, it was found a significant decrease in serum levels in 48hrs and at 3 to six weeks,(p-value <0.0067) this shows a possibility of good outcomes after surgery. A follow up of six month was not adequate for objective conclusion.

Among 42 patients who were reviewed, 59.5% had Hardys Classification grade II, 35 patients were treated surgically and 6patients with prolactinomas were treated medically, and one patient died while waiting operation with pituitary apoplexy. Sixty four percent of patients who had transphenoidal surgery had improvement, 4(80%) who had transcranial route, had improvement and there was statistical significant (p-value< 0.060). Considering all surgical modality used in all 35 patients who only 25.7% had no residual tumours and 74.3% had residual tumours. As far as surgical approach is concern, there was no statistical significance among surgical treatment approach used (p-values <0.27).

Every surgical treatment had complications post operatively, however the patient who were operated transphenoidally had more complication than other group and this could be due the fact that 67% of patient who were operated had transphenoidal surgery, overall complications were CSF leak s(14.3%),DI (14.3%), Meningitis (8%)and permanent hypopituitarism (29.6%.)Other patients who had residual tumours were either reoperated, treated medically with adjuvant therapy or stereotactic radiotherapy.

Conclusion: Medical treatment for prolactin secreting tumours, and Surgical treatment for GH, ACTH, and TSH secreting tumours remain the known modalities of treatment of choice for pituitary adenomas. However sample size was small and findings of this size merit further research.

Recommendations: Education is needed to avoid late hospital presentation to prevent avoidable irreversible visual disturbances. There is a need of the IALCH to improve its record keeping. Standardized criteria are of importance in managing patients with residual tumours

TABLE OF CONTENTS

CERTIFICATION	**ii**
DECLARATION AND COPYRIGHT	Iii
ACKNOWLEDGEMENT	iv
DEDICATION	v
ABSTRACT	Vi
LIST OF TABLES	viii
LIST OF ABREVIATIONS	x
CHAPTER ONE	
1.1 Introduction	
1.2. Literature review	3
1.2.1. Diagnosis of Pituitary Adenoma	5
1.2.2. Imaging	6
1.2.3 Blood Analysis	7
1.2.4. Treatment of pituitary adenomas	8
1.2.5. Medical treatment	9
1.2.6 Surgery in Pituitary adenomas	9
1.2.7. Radiotherapy	11
1.2.8. Prognosis of pituitary adenomas	11
CHAPTER TWO: PROBLEM STATEMENT AND RATIONALE	
2.1. Problem statement	13
2.1.1. Conceptual frame work	14
2.2. Rationale	14
2.3. Research Hypothesis	15
2.4. Broad Objective	15
2.5. Specific objective	15

CHAPTER THREE:METHODOLOGY

3.1.Study design 16

3.2. Study area 16

3.3. Study population 17

3.4. Inclusion criteria 17

3.5. Sample size 17

3.6. Data Collection 17

3.7. Data Analysis 17

3.8. Exclusion criteria 18

3.9. Definition of terms 18

3.9.1. Outcome 18

3.10. Ethical consideration 18

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1. Results 19

4.2.Discussion

CHAPTER FIVE : CONCLUSION AND RECOMMENDATION

5.1. Conclusion 39

5.2. Recommendation 39

5.3. Limitation of the study 39

40

REFERENCES

Appendix 1 43

Appendix 2 50

Appendix 3 51

LIST OF TABLES

Table	Contents	Page
Table 1	Age and Sex distribution table	19
Table 2	Distribution and duration of symptoms in patients presented with pituitary adenoma	20
Table 3	Distribution of symptoms and signs in patient who had GH secreting tumour	21
Table 4	Distribution of symptoms and signs in patient who had Cushing disease	22
Table 5	Distribution of Prolactin secreting Hormone serum levels in prolactinomas at time of diagnosis and at 3 to 6 month after treatment	23
Table 6.1	GH hormone secreting tumours IGF-1 level at diagnosis and 48hrs after operation	24
Table 6.2	Growth Hormone levels before at diagnosis and 6 weeks after operation	25
Table 7	Radiological classification of pituitary adenoma by Hardys Classification	25
Table 8	Distribution of indications of surgery	26
Table 9	Surgical approach and their outcomes	27
Table 10	Association between Surgical approaches and complications	28
Table 11	Histological distribution of pituitary adenoma operated at IALCH	30
Table12	Association between Grade and surgical treatment approach	31
Table12	Association between surgical treatment approaches and residual tumour	33

LIST OF ABBREVIATIONS

ACTH- Adrenocorticotropic hormone

BMP-4- Bone Morphogenic Protein

CSF- Cerebral Spinal Fluid

CT- Computer Tomography

DI- Diabetic Insipidus

DSA-Digital Substraction Angiography

FGF-8- Fibrous Growth Factor -8

GH- Growth Hormorne

ICP- Intracranial Pressure

IALCH- Inkosi Albert Luthuli Central Hospital

KZN-KwaZulu Natal

IGF-1- Insulin –like growth factor -1

LH- Lutenizing Hormone

MRI- Magnetic Resonance Imaging

OP - Operation

PA- Pituitary Adenoma

PRL- Prolactin

RNA-Ribonucleic Acid

TSH- Thyroid Stimulating Hormone

UKZN- University of Kwazulu Natal

CHAPTER ONE: BACKGROUND

1.1 INTRODUCTION

Pituitary tumours are common neoplasms and recognition of the presentation is critical since favourable outcome dependents on early recognition. Pituitary Adenoma was first described in French in 1886 by Pierre Marie in two acromegaly patients and it was postulated that pituitary gland was involved in the pathogenesis. (2)

Multiple oncogene abnormalities may be involved in pituitary tumour pathogenesis. G-protein abnormalities, as gene mutations and p-53 gene deletions, mutations and rearrangements and the association of pituitary tumours with syndrome of multiple endocrine neoplasia (MEN) have been described and involved in the development of adenomas in pituitary gland.

It has been recently suggested that pituitary tumorigenesis is more heterogeneous than formerly thought. Hypermethylation of p16 has been associated with non functional adenenomas, whereas prolactinomas and corticocotropin-secreting tumours express galectin 3 (Gal-3), a gene involved in cell growth and apoptosis. Mutations of aryl hydrocarbon-interacting protein gene (AIP) may be present in some cases of familial gigantism and acromegaly, as well as other pituitary tumours types.

Majority of pituitary tumours are benign, but certain factors involved in tumour pathogenesis may determine its rate of growth and aggressiveness. For example presence of p53 tumour gene has been correlated with more aggressive tumour behaviour

Historically, pituitary tumours have been classified according to size and divided into two main groups, i.e. microadenoma (<1cm) and macroadenoma (>1cm). This classification has been also augmented by a more comprehensive system based on immunohistochemistry and electronic microscopy as functional and non-functional depending on their hormonal activity in vivo. (11)Those microadenomas which are hormonary inactive are rarely diagnosed or found as incidental findings in radiological investigations and post-mortem examinations whereas a same small tumour but hormonary active are early diagnosed because of their early presentation as clinical syndrome (26).

For Macroadenomas they are late diagnosed because are slow growing and when they are diagnosed is because of intracranial mass, pressure effect on vital structures like optic chiasma and pituitary stalk etc [1, 11, 24].

Histological diagnosis, lab results, CT scan, MRI of those patient who have been treated of the pituitary tumours or related condition is a main way of studying the disease clinical presentations treatment modalities, complications and recurrences. [11, 12]

Prevalence of Pituitary adenoma vary from area to area, in Europe it is estimated to be 78 to 94 cases 100,000 inhabitants this is from epidemiological data from Swistzerland, Belgium and United Kingdom, but in North Finland it shows overall standardized incidence rate of 4 per 100,000.[29]

In Mlindermam study, females are more affected than males, and ACTH releasing adenoma, TSH, releasing adenoma, occurs in female while endocrine inactive and GH releasing adenomas occurred most in males. [30] It has been noted that for prolactinomas the peak occurrence was 2nd to 5th decade of life and for endocrine inactive adenomas in 4th and 8th decade but for GH-releasing, ACTH, and TSH releasing adenomas they are usually more evenly distributed through the life span.[30]

1.2. LITERATURE REVIEW

Prevalence of pituitary adenoma is estimated to range from less than 1% to more than 30%.Given the small size of many of pituitary tumours and their ability to exist with or without symptoms, or with only insidious, nonspecific symptoms it a big challenge to study pituitary adenoma in general population [11].

Pituitary adenomas are classified into two main groups, non function and functional. Non functional pituitary adenoma is a most common group contributing to about 60 % of pituitary adenoma while functional contributes about 30% [1]. Prolactin-secreting adenomas (prolactinomas) account for approximately 30% of pituitary adenomas and 50 to 60% of functional pituitary tumours. They are the most common type of functioning pituitary tumour and are second in frequency to non functioning adenomas in overall incidence.[1]

Asymptomatic pituitary adenomas are relatively common and can present as incidental findings upon autopsy or radiography. Symptomatic tumours typically present with mass effects in the region of the sella turcica or with endocrine dysfunction, but can also present as an urgent compressive condition due to intratumour haemorrhage or infarction, a condition known as pituitary apoplexy [14, 23].

The symptoms due to the mass effects of these tumours depend on the structures compressed. Direct intrasellar compression of the anterior pituitary can cause endocrine hypofunction.

If hypofunction occurs due compression the most affected hormone is GH followed by gonadotropins, TSH, and then ACTH, however symptom and sign of low GH are rare detected clinically. Also during hypofunction it is uncommon to find only single hormone is affected, and if only one hormone is affected it important to rule out extra cranial course.

In Suprasellar compression onto the optic chiasm can cause visual field deficits, most classically bitemporal hemianopsia in about a third of patients with radiographic evidence of compression [1, 2] . Those patients with compression of the third ventricle can present with hydrocephalus (and other features of raised ICP).

When the pituitary adenoma expands laterally may lead to compression of cavernous sinus and structures within the cavernous sinus, including cranial nerves III, IV, V_1, and V_2. Symptoms are unusual to have, but these patients can present with ophthalmoplegia, ptosis, facial pain and diplopia [2].

In patient whereby tumour has compressed the pituitary may lead to hypothalamic disinhibition of PRL secretion and moderate hyperprolactinemia (the so-called "stalk effect") [23]. Headaches in Pituitary adenoma cases are common, with estimates ranging from 33% to 72% of patients presenting with some sort of headache.

However its cause is still controversial, some author associate it with interstellar pressure, possibly due to compression of V_1 on the sella dura, the tumour size or inversion of cavernous sinuses have no correlation with headache. Also Headache pathogenesis has also been speculated to work through a hormonal rather than pressure-related mechanism [1].

Apart from mass effect, in hypersecretory pituitary adenomas patient will present with symptoms with findings typical of hormonal hypersecreted. Prolactinomas may present with impotence and decreased libido in men, amenorrhea and galactorrhea in women. They can lead to infertility and bone loss in both sex. Because of their more specific symptoms, women with prolactinomas are often diagnosed earlier in their disease course than are men [3, 23].

Somatotropic adenomas are the predominant cause of elevated serum GH and thus patients with these tumours will present with findings typical of acromegaly in adults or gigantism in children. Acromegaly is marked by the insidious progression of skeletal and soft tissue enlargement. Also Connective tissue, cartilage, bone, skin, and viscera can all be affected. Among the more serious complications of acromegaly are upper airway obstruction due to enlarged structures, peripheral neuropathies such as carpal tunnel syndrome, large joint arthropathy, diabetes mellitus, and biventricular cardiac hypertrophy leading to diastolic heart failure, other cardiovascular diseases, and colon cancer [3, 6, 18].

ACTH-secreting tumours will present with Cushing syndrome (hypercortisolism), characterized by hyperglycaemia, hypertension, osteoporosis, central obesity, increased supraclavicular and dorso-cervical fat pads (the so-called "buffalo hump") and excessive hair growth in women. Patients with a history of bilateral adrenalectomies can also present with signs of Nelson syndrome.

They may have signs of tumour enlargement and skin hyper pigmentation (due to increased levels of melanocyte-stimulating hormone). This is thought to be due to increased growth of ACTH-secreting pituitary adenomas in the absence of inhibitory feedback from the adrenal glands.

Thyrotrophic adenomas are the cause of central/secondary hyperthyroidism, and will present with high or inappropriately normal TSH levels in patients with elevated circulating levels of thyroid hormone [3].

These patients manifest signs of hyperthyroidism, including unintentional weight loss, anxiety, heat intolerance, hypoglycaemia, tremors, and hyperactivity.

They are very rare tumours but tend to be more aggressive and invasive than others.

In pituitary apoplexy, tumours haemorrhage or infarct in the sella turcica, rapidly swell, and then cause rapid compression of surrounding structures. Larger adenomas are thought to be of higher risk of apoplexic events. It is an uncommon first presentation of Pituitary tumours but has been reported in as many as 17% of cases [7, 15, 16]. Patients with pituitary apoplexy present with the rapid onset of many of the mass effects discussed earlier, including pituitary insufficiency (such as adrenal insufficiency and/or diabetes insipidus); headaches; visual disturbances (with ophthalmoplegia being more common than bitemporal hemianopsia, are reversal of the incidences seen in more gradual compression); altered mental status and loss of consciousness (especially with hypothalamic involvement); and if haemorrhage escapes the tumour capsule, possible increased intracranial pressure due to subarachnoid spread of blood [15,16]. Subacute cases of pituitary apoplexy can go on to cause more subtle hypopituitarism. It is important to recognize pituitary apoplexy rapidly and provide appropriate surgical and medical treatment (typically need to decompress the sellar in 24 hours) as the patient's condition can rapidly worsen [9, 10].

1.2.1. Diagnosis of pituitary adenomas

When considering the possibility of pituitary adenomas suspicion should be raised in patients with endocrine hyperfunction, multiple endocrine hypofunction, visual field deficits, or cavernous sinus cranial nerve deficits. Diagnosis is typically achieved through a combination of imaging and endocrine laboratory tests.

Imaging is typically an early step in the diagnostic workup, with MRI being the test of choice, along with an endocrine panel assessment [2].

Goals of imaging are to evaluate the pituitary gland itself, including the presence of masses within the gland, and to evaluate for parasellar infiltration, including those involving the pituitary stalk, suprasellar region, and hypothalamus [20, 21].

1.2.2. Imaging

Normal pituitary on unenhanced T1-weighted MRI scans; there is a normal "bright spot" in the posterior gland (neurohypophysis), which is thought possibly to be related to storage of vasopressin or related compounds.

A strong enhancement of the pituitary gland and stalk after contrast administration is normal; microadenomas are usually hypointense to the gland on T1-weighted imaging and variable appearance on T2-weighted. Most commonly, they are isointense (i.e., not distinguishable from background tissue). Some may be hyperintense, but low T2 signal may be evident in hemorrhagic or more fibrous lesions [(2)].

Macroadenomas commonly are more hyperintense than glandular tissue on T2-weighted images. Microadenomas are generally confined to the gland, and although they may distort the contour of the gland, because of their small size they do not generally result in mass effect. Macroadenomas, on the contrary, typically come to clinical attention because of their mass effect, so extension outside the sellar at the time of imaging is common. Classically, there may be a waist formed in the macroadenoma as it passes through the diaphragm sellar, leading to the "snowman" appearance. Evaluation of patients with Macroadenomas should include assessment of the degree of mass effect on the suprasellar structures, invasion of the cavernous sinuses, and involvement of the sphenoid bone and sphenoid sinus [(14)].

The contrast-enhancement patterns of adenomas depend on the interval between contrast administration and imaging. The majority of microadenomas take up contrast more slowly than the surrounding gland, so they usually are hypo enhancing compared with the background pituitary tissue. The use of contrast improves sensitivity for the detection of microadenomas compared with unenhanced imaging [(14)].

Angiography may be need in case the surgeon needs to clarify the anatomy of parasellar carotids that are suspected to be more medially located ("kissing carotids").

CT angiography and MR angiography are used before digital subtraction angiography (DSA) because these modalities are non-invasive as well as safer, cheaper, and often easier to perform than DSA.

Even in patients who have undergone MRI, some surgeons recommend obtaining preoperative facial CT scans to assess the bony anatomy of the sphenoid sinus for help in guiding proper trajectory during transphenoidal resection. These images may also be integrated into neuronavigation systems for the same purpose [28]

Negative CT and MRI studies do not exclude the possibility of microadenoma. Secretory pituitary adenoma, most commonly those responsible for Cushing disease, can be symptomatic even at very small sizes (e.g., 1–2 mm) [11].

In patients with symptoms suggestive of a secretory pituitary adenoma but have negative imaging study, endocrine testing should still be performed to evaluate the possibility of functional micro adenomas.

1.2.3. Blood analysis

Endocrine testing is also useful to confirm that presenting symptoms are pituitary in origin and, also results can have implications for treatment options Inferior petrosal sinus sampling can also be performed to confirm the diagnosis of Cushing disease and determine the laterality of a microadenoma not detected on imaging [13]. When analyzing Prolactin (PRL) levels, it is important to keep in mind that values can be elevated due to a number of conditions other than pituitary adenoma. Patients with elevated PRL levels should also be screened for pregnancy; specific drugs (e.g., oral contraceptives, metoclopramide, verapamil, opiates, and many antipsychotics such as haloperidol, phenothiazines, and resperidone); primary hypothyroidism; chronic liver disease, which may be oestrogen-mediated rather than a direct effect; and renal disease [6].

PRL levels can be elevated by two different mechanisms in patients with pituitary adenomas: by a PRL-secreting tumour or compression of the pituitary stalk by a large tumour. The stalk effect is usually only associated with moderately elevated PRL levels (25–150 ng/mL), whereas prolactinomas typically show higher elevations (150 ng/mL). Notably, very high levels of PRL can also overwhelm some assays, producing a falsely low reading (the “hook effect”). If a prolactinoma is suspected, serial dilutions of the sample can be used to avoid the hook effect and ensure accurate results. Therefore, anytime the PRL level is higher than 150 ng/mL, the laboratory should be instructed to perform serial dilutions to ascertain the level [3, 23].

In considering possible cases of acromegaly or gigantism, it’s important to bear in mind that as GH is secreted in a pulsatile fashion across the day.

Apart from GH levels other test which can be done do diagnose a growth hormone secreting tumours is by doing blood for insulin- like growth factor 1 (IGF1) levels or an assessment of GH suppressibility via an oral glucose tolerance test (OGTT) can be used [(3).]

When a patient present with features suggestive of Thyroid secreting hormone tumour, then Thyroid-stimulating hormone (TSH), free T4, and perhaps free T3 levels should be measured in the blood. It also important to note that patient may present with features of hypothyroidism may be detected in screening of other pituitary tumours.

When a functional or non-functional pituitary macroadenoma is diagnosed via imaging, formal ophthalmology evaluation should be obtained to assess visual fields (e.g., Goldman perimetry testing) and to exclude other causes of visual disturbance. This will form a baseline for feature assessment of improvement or deterioration of the patient after surgery or medical therapy. In patients with untreated macroadenoma, changes from baseline visual fields may be evident before there is any noticeable change on images [()].

1.2.4. Treatment of pituitary adenomas

Surgery is typically the first-line treatment for most patients with symptomatic pituitary adenomas as they generally respond poorly to currently available medical therapy except for prolactinomas. In Prolactin (PRL)-secreting tumours, medical management with dopamine D2 agonists such as bromocriptine (typically 5–30 mg/d over 3–4 doses), pergolide (0.05 0.25mg/d over 1–2 doses), or cabergoline (0.5–2.0 mg/wk over 2 doses, higher D2 specificity) is preferred. Treatment can last several years but typically is effective quickly, with 80% to 90% of patients normalizing their serum PRL concentrations after only a few weeks, and 70% experiencing tumour shrinkage within 3 to 6 months.

Surgery can be considered in failed medical management or if medical management is poorly tolerated or contraindicated, or is complicated by poor adherence [(3, 4, 5).]

Non-symptomatic, non-secretory tumours do not necessarily require surgery. Patients with asymptomatic microadenomas are typically observed with imaging at 1-, 2-, and 5-year intervals to evaluate for further growth. Treatments with dopamine agonists or somatostatin analogs have shown only modest reductions in tumour size for non-secretory Macroadenomas, but these drugs may be useful in the setting of neoadjuvant therapy [(1)].

1.2.5. Medical treatment

Medical management for patients with all other types of pituitary adenoma is considered only in those who cannot tolerate surgery, or un-resectable tumour recurrences, or in patients for whom surgery is non-curative.

In these instances, drug choice is based on tumour type. Somatotropic adenomas can be treated with dopamine agonists or, preferably, a somatostatin analog such as octreotide. A total of 80% to 90% of patients treated with octreotide will experience a decrease in serum growth hormone (GH) and plasma insulin-like growth factor (IGF)-I concentrations, but only in 50% to 60% of patients will those values return to normal ranges (30%–40% will also see a moderate reduction in tumour size the of treatment of GH secreting tumours should aim at reducing GH levels and this has been found to decrease the mortality rate significantly [3,7,8].

In patients with Cushing disease, endogenous corticosteroid production can be lowered with ketoconazole, metyrapone, mitotane, or cyproheptadine. Ketoconazole (600–1200 mg/d) is a popular drug of choice as it is relatively less expensive, safer, and more efficacious than other therapies. Approximately 70% of patients experience a reduction in serum cortisol levels, but long-term use can lead to hepatotoxicity. Patients with thyrotrophic adenomas can be medically treated by use of octreotide (lower dose: 50–100 mcg daily) and symptoms managed with agents such as beta-blockers and perhaps low-dose antithyroid medications. Octreotide treatment is effective in lowering thyroid-stimulating hormone (TSH) levels in 80% to 90% of patients but succeeds in slowing tumour growth in only 30% [].

1.2.6. Surgery in Pituitary Adenomas

Surgery for symptomatic non-PRL-secreting tumours is the first-line option for patient management. Surgical approaches are either transphenoidal or trans-cranial, with complete resection being possible in the vast majority of cases. Microsurgery via a transphenoidal approach is the usual option of choice for several reasons: less morbidity, no brain retraction, no external scarring, faster and more direct approach. It is indicated for microadenomas and most Macroadenomas. This approach may provide better chance of gross total resection, in Sudhirs study this was achieved in 38% of patients [(1)].

A trans-cranial approach is indicated in patients with extension of the tumour into the middle fossa (typically pterional craniotomy) or extensively into the suprasellar region (typically bifrontal craniotomy).

If the transphenoidal approach is contraindicated, for example, if the patient has a parasellar aneurysm; if a previous transphenoidal approach failed because of a firm tumour; or in the setting of tumour that was medically treated and therefore may have become firm then transcranial approach can be used. A transcranial approach is associated with poorer outcomes, including new pituitary deficits (15%), greater chances of persistent postoperative diabetes insipidus (DI) (3.2%), and increased rates of intra-operative mortality (2.3%).

Endoscopic resection through a transphenoidal approach has become a popular alternative to microsurgery [(14).]

Thus, having the option of endoscopy may reduce the need for transcranial surgery in some cases. The results of the technique show some promise, with investigators reporting a 79% gross total removal rate in patients with non-functional Pituitary adenomas and comparable biochemical cure rates in those with PRL-secreting (66%), adrenocorticotropic hormone (ACTH)-secreting (72%), and GH-secreting (85%) tumours [(14).]

Complications experienced are similar to those experienced in traditional microsurgery, such as permanent DI (3%), pituitary insufficiency (14%), cerebrospinal fluid (CSF) leakage (2%), and sinusitis (2%).

Some of few Pituitary adenoma may present with the acute onset of headache (93%); defects in visual acuity, visual fields, or ophthalmoplegia (75%); and compromised anterior Pituitary function (67% adrenal, 45% thyroidal) and this is called pituitary apoplexy. Other general symptoms include nausea, vomiting, and altered mental status (secondary to hypothalamic involvement, DI, or chemical meningitis). Upon diagnosis, patients should undergo endocrine evaluation and initiation of critical replacement hormones [(10, 15, 16)].

Although peri-operative mortality is rare (1%), a number of complications from pituitary tumour surgery can arise. One of the most common is DI resulting from damage to the Pituitary stalk or posterior pituitary. The condition can be transient, permanent, or triphasic (with normalization of an original response and secondary recurrence).

Onset is typically within 24 to 48 hours postoperatively and permanent DI is uncommon (3.8%) and in other study it has been reported 8.7% of patient of DI persisted for more than 3 month [27].

Other common complications include nasal septal perforation (7.6%), postoperative CSF leak (2.3%), donor site hematoma after harvesting fat graft (2.2%), residual tumour haemorrhage (1.6%), ophthalmoplegia (1.1%), and loss of vision (1.1%).

Hypopituitarism may result from surgery, especially in instances of repeat surgery or in patients who have received radiotherapy. In such settings, appropriate hormone replacement therapy should be instituted.

1.2.7. Radiotherapy

Radiotherapy is not recommended for first-line therapy and is also not routinely used after surgical resection. It has rarely been used but might be considered in patients with un-resectable disease, or when other therapeutic modalities have failed and there is a need to attempt to reduce secretory production. The most commonly experienced complication is hypopituitarism, with up to 72% of patients experiencing pituitary insufficiency post-radiotherapy. Patients may also experience optic nerve/chiasm/tract damage, memory disturbances, cranial nerve palsies, and even tumour necrosis and subsequent apoplexy. The response of tumours to radiation varies by tumour type, with prolactinomas showing the least response and other types showing better responses [23]. Therefore the role of radiotherapy in treatment of pituitary adenomas remains limited in light of potential toxicities and the efficacy of medical and surgical management in many patients.

1.2.8. Prognosis of Pituitary adenomas

In general, prognosis for patients undergoing pituitary adenoma surgery is excellent but varies with tumour type. For example, complete tumour removal and hormonal normalization is achieved in 85% to 90% of patients with microprolactinomas, 60% to 70% of patients with macroprolactinomas confined to the sella, and less than 50% of patients harbouring prolactinomas with extrasellar extension. In the study by Peter GC et al in patients with acromegally the biochemical cure(i.e. IGF and suppression of GH) was achieved in 50% for endoscopic adrenectomy was 57% and better cure rates were seen in small tumours [17].

In 80% to 85% of patients with ACTH-secreting tumours, complete removal is achieved with subsequent normalization of cortisol secretion [19].

In non-secretory pituitary adenomas tend to be lower cure rate as they are typically larger at time of diagnosis. For patients with pituitary tumours of all types that undergo therapy, the recurrence rate varies between 9% and 19%, and most commonly occur in the 5- to 9-year range.

Few studies have evaluated the impact of surgery on headache alleviation, but the existing evidence does point to some efficacy. Tumour resection was reported to improve headaches in 74% of patients in a small study of microadenomas and macroadenomas and in 87% of patients with microadenomas in another study. The exact mechanism of pain relief in these patients has yet to be known [21, 22].

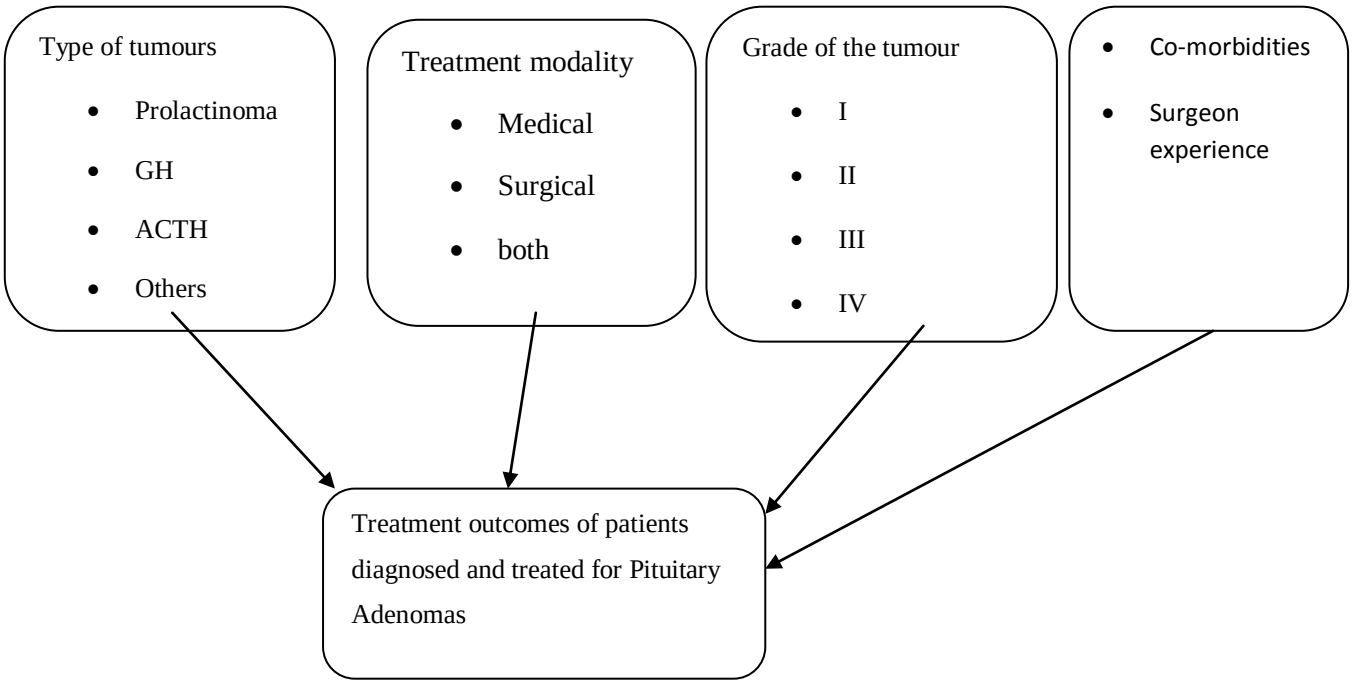
CHAPTER TWO: PROBLEM STATEMENT AND RATIONALE OF THE STUDY

2.1. Problem statement

Pituitary adenomas are common problem in our communities with estimated prevalence ranging 1-30% however the extent of the problem at UKZN is not well known.

Effective treatment of patients with pituitary adenoma requires communication and cooperation among several medical specialists including physician, neurosurgeon, endocrinologist, neuroendocrinologist, neuroradiologist, ophthalmologist and radiotherapy physician. There is evidence that, high index of suspicion, early diagnosis and early treatment can avoid many complications and neurological deficit caused by the pituitary adenomas. As far as pituitary adenomas is concerned, there are very few literatures on treatment outcomes of patients who were diagnosed and treated for pituitary adenoma at KZN in relation to the treatment modality (medical, surgical or both), type of tumour and grade of tumour. Therefore, the purpose of this retrospective study is to find out treatment outcomes of patients who were diagnosed to have pituitary adenomas following different treatment modalities. Depending on the study findings, department of Health of KZN will be advised on cost effective and cost efficient approach in managing patients with pituitary adenomas as well as if there will be a need to influence change in practice. Information obtained from this study will also provide guidance on public health intervention.

2.1.1 Conceptual frame work



2.2. Rationale

Good outcome following treatment of pituitary adenoma remains key in improving the quality of life for patients diagnosed and treated for such tumours. However, favourable outcome depends on early recognition of symptoms, diagnosis and instituting the right treatment modality depending on the stage and type of the tumour.

This study will delineate, different clinical presentations, diagnosing modalities and different medical and surgical treatments approach and their outcome in patient seen at IALCH and provide information on the magnitude of the problem and suggest ways to early case detection and advice on patients care. It is also done as part of a partial fulfilment of Master of Science requirement in Neurosurgery programme.

2.3. Research Hypothesis

Transphenoidal surgery for pituitary adenoma has poor success rate and reoperation is required in most of the patients.

Transphenoidal surgery for pituitary adenomas is associated with bad outcome compared with other treatment modalities.

2.4. Broad objective

To determine treatment modalities of pituitary adenomas and their outcomes at IALCH between Jan 2007 to December 2012;

2.5 .Specific objectives

1. To determine trends of signs and symptoms of pituitary adenomas

2. To determine the radiological classification of pituitary adenomas by Hardy's classification

3. To determine the trends of endocrine profiles at diagnosis and after treatment for hormonally active tumours treated medically and surgically.

4. To determine indications of different surgical treatment modalities.

5. To determine the histological patterns of pituitary adenomas

6. To determine the outcomes of surgical treatment modalities used.

7. To determine the association between surgical treatment options and residual tumour of pituitary adenomas

CHAPTER THREE: METHODOLOGY

3.1. Study design

This was a retrospective cross-sectional review of patients who were diagnosed from different hospitals and referred to IALCH for definitive treatment between Jan 2007 to December 2012. Patients record were retrieved and thorough review was done, those who met inclusion criteria were reviewed to the follow up period of 6 months for both patients treated medically and surgically. It is accepted that for any patient who was either operated or treated medically, a follow up of six months will have shown an impact on patient's pre-morbid condition. Therefore follow up in all patient's clinical notes were critically reviewed for six months after initial definitive treatment.

3.2. Study area

Inkhosi Albert Luthuli Central Hospital (IALCH)

Inkhosi Albert Luthuli Central hospital is a 1000 bed super specialized quaternary paperless referral hospital with state of the art facilities.

The Neurosurgery unit consist of 110 beds (Paediatric and Adult) including 6 neurosurgical intensive care bed and 7 high care beds. The Paediatric neurosurgical unit has 18 beds with high care beds, septic and isolation units.

It serves a catchment area of population of approximately 12 million people (KZN and part of Eastern Cape) and provides emergency and elective treatment in all disciplines of neurosurgery.

The hospital has a unique neurosurgical referral pattern using the telemedicine system which provides a link to at least 10 major hospitals equipped with CT and MRI facilities. The hospital has 19 operating theatres supported by 75 intensive care and 96 high care beds. The neurosurgical units have two fully dedicated operating theatres with neuroanasthetists. Approximately 1000 surgical interventions are performed every year (cranial and Spinal).

The operating theatre and intensive high care units are equipped with state of art facilities (Neuronavigation, stealth system, 2 operating microscopes, Nueroendoscopic tower and two state of the art angiographic onsite for neuroendovascular procedures.

Patients with wide varieties of pathology are treated in the unit. These include neurotrauma, neurosepsis, neoplasms, vascular pathologies, endovascular interventional treatment, spinal pathology and paediatrics pathology. The hospital is an excellent academic centre and has a rigorous and well elaborated teaching and training for neurosurgical residents more than 10 usually span 3 to 4years before doing the neurosurgical fellowship examination.

3.3. Study Population: All patients who were diagnosed to have pituitary adenoma and confirmed histologically from Jan 2007 to December 2012 were included.

3.4. Inclusion criteria:

All patients aged between 19 years to 76 years who have been diagnosed to have pituitary adenoma by, clinical examination, radiogical, and laboratory and confirmed by histology from Jan 2007 to December 2012

3.5. Sample size: Patients who had pituitary adenomas between Jan 2007 to December 2012

3.6. Data collection: Medical records of each patient were reviewed and details transferred to a data abstraction tool. All patients' information from the first visit, treatment, follows up and any adjuvant treatment was extracted from the data abstraction tool to the Microsoft excel data sheet. Patient data on first admission and pre-operation were recorded and patients' records on follow up visits within six months were also recorded.

3.7. Data Analysis: All filled Data abstraction tools were given identification number before entering into Epi info 6/ data package systems, data cleaning was done and frequency table drawn ,Cross tabulations was done for independent variables to obtain table results. Then Chi-Square test-values and frequency were calculated.

3.8. Exclusion criteria: Lost to follow up patients were excluded from the study.

Patient whose follow up was less than six month will be excluded**.**

3.9. Definition of terms

3.9.1. Outcome: Regarded as clinical condition after treatment whether medical or surgical and their complications, this is taken from a day of definitive treatment initialization to up to six month

3.9.2. Improved: In this study is regarded as improvement in presenting clinical symptoms and signs, i.e headache or Visual disturbance in patient who where treated medically and surgically.

3.9.3. No improvement: regarded as no change in patient's preoperative clinical condition or deterioration of his or her clinical condition after medical or surgical treatment

3.9.4. No residual tumour is considered when a post operative MRI is done in 3 to 6 month time and the reporting radiologist compared it with a preoperative MRI and concluded **"No significant residual"**

3.9.5. Residual tumour is when the preoperative MRI was compared with post operative MRI in terms of preoperative dimensions of the tumour and post op 3 to six month post operative MRI and the radiologist concluded " **significant residual"**

3.10. Ethical issues and Permission to conduct a research: Ethical clearance was sought from Inkhosi Albert Luthuli central Hospital ethical committee

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1 RESULTS

This study was a cross-sectional retrospective review of patient's records from Jan 2007 to Dec 2012. A total 42 patient records were reviewed after meeting the inclusion criteria. Twenty Eight (67%) were females and 14 (33%) were male , Male to female Ratio was 1:2.(P value <0.15) Nearly above 50% had age above 40 years, mean age was 43yrs with a range of 19 years (minimum) to 76 years (maximum) and median of 40years, among males 6(21.4%) patients were at the age group between 49 to 58 years and Among females 10 (35.7%) were between 39 to 48 years age group. The most affected age group was 43-48years which constituted 31% of the patients (Table 1. below).

Table1. Age and sex distribution table

Age group(yrs)	**Male**	**Female**	**Total**
	n (%)	**n (%)**	**n(%)**
18-28	2(14.3)	6(21.4)	8(19)
29-38	2(14.3)	6(21.4)	8(19)
39-48	3(21.4)	10(35.7)	13(31)
49-58	6(42.9)	2(7.2)	8(19
59-68	1(7.1)	3(10.7)	4(9.6)
>69	0(0.0)	1 (3.6)	1(2.4)
Total	**14(33)**	**28(67)**	**42(100)**

P-value=0.15

Among 42 patients record reviewed the commonest presenting symptoms were Visual disturbance in 30 (48.4%), headache in 19(30.6%), Amenorrhea in 5(8.1%) and loss of libido in 3(4.8%). Also it important to note that other patients presented with more than one symptom (table 1.2 below). Of those 30 patients who presented with visual disturbance 14(46.6%) had that symptoms for about 7-12months, 9 (30%) had poor vision for less than 6month and 3(10%) had Visual disturbance for more than 25month (table 2. below)

Table 2. Distribution of general symptoms and duration of symptoms in patients presented with pituitary adenoma

Symptoms	**Number**	**Percentage (%)**
Headache	19	30.6
Visual disturbances	30	48.4
Amenorrhea (♀)	5	8.8
Decreased libido	3	4.8
Impotence(♂)	0	0.0
Galactorrhea	4	6.5
Gynaecomastia	1	1.6
Duration of visual disturbances(Mon)		
<6	9	30
7-12	14	46.6
13-18	2	6.7
19-24	2	6.7
>25	3	10

Among 45 patients reviewed 8 had acromegalic features, on presentation frequently picked symptoms were facial pain, sleep apnoea, joints pain and excessive sweating, the most common sign noted on examination was upper and lower limb enlargements 30.3% (table3 below). However there were other patients who had acromegalic features but were no clinically acromegalic (table 3 below). Two patients, Female (19years) and male (24years) had Cushing disease had weight gain as one of their complaint, which was confirmed during physical examination; however there were other patient noted to have weight gain. A male (Cushingoid) patient was initially diagnosed at the age of 8years, under gone transphenoidal surgery 3 times, followed by bilateral adrenolectomy at the age of 15 years, his recent presentation was as a case of Nelson syndrome (table 4 below).

Table 3. Distribution of symptoms and signs in patients who had Growth hormone secreting tumor

Symptoms	**Number**	**Percentage**
Facial pain	6	25
Sleep Apnoea	6	25
Facial pain	6	25
Excessive sweating	6	25
Signs		
Frontal bossing	7	23.3
Large beefy hands and feet	9	30.3
Coarse facial features	5	16.7
Skin tags	6	20
Increased spacing between toes	8	26.7

Table 4. Distribution of signs in patients who had Cushing disease.

Sign	Number	Percentage
Muscles weakness	1	7.1.
Hypertension	1	7.1
Weight gain	4	28.4
Facial plethora	1	7.1
Supraclavicular fat deposit	1	7.1
Acantosis nigricans(acne)	1	7.1
Hirsuitism	2	14.2
Violaceous stria	3	21.4

Six (14.3%) patients had prolactinoma at the time of diagnosis and treated medically, 4 (66.6%) patients had serum prolactin levels between 50000 to 1000001 ng/ml at the time of diagnosis and were treated with bromocriptine and carbagoline, at 3 to 6month follow MRI showed significant tumour reduction, patients vision improved and serum prolactin levels were 2001 t0 3000ng/ml (P-value< 0.040). Also a patient who was on bromocriptine had drug induced psychosis and was changed to cabergoline (table 5 below).

Table 5. Distribution of Prolactin hormone serum levels in prolactinomas (At time of Diagnosis and 3 to 6 month after medical treatment)

Serum prolactin range (ng/ml)	**Number**	**Percentage**
At Diagnosis		
10000-25000	2	33.3
25001- 50000	0	0.0
50001-75000	2	33.3
75001-100000	2	33.3
3 to 6month after treatment		
1000-2000	1	16.7
2001-3000	3	50
3001-4000	0	0.0
40001-5000	2	33.3
Total	**6**	**100**

P-value =0.045

Amongst 8 patients who had Growth Hormone secreting tumor 5(62.5%) had IGF-1 level above 1101ng/ml at the time of diagnosis and 5(62.5%) had IGF-1 levels ranging 500-800ng/ml in serum specimen taken within 48hrs after the operation (P- value <0.11) (table table 6.1 below).

Table 6.1. Growth Hormone secreting pituitary adenomas IGF- 1 levels at time of Diagnosis and 48rs after operation

IGF-1 range(ng/ml)	**Number At Diagnosis (%)**	**Number 48hrs after operation (%)**
500-800	2(25)	5(62.5)
801-1100	1(12.5)	2(25)
>1101	5(62.5)	1(12.5)
Total	**8(100)**	**8(100)**

P-value =0.11

Amongst 8 patient who had GH secreting tumours, 6(75%) at the time of diagnosis had serum GH levels more than 91ng/ml and at six weeks after operation the serum level decrease to less 10-30 ng/ml in 6(75%) of the patients(P- value <0.006). Also two patients who had GH secreting tumour and were Acromegalic had positive OGTT test while the other six patients presented with Diabetic mellitus so the OGTT was not done. Among 8 patients who had GH secreting tumours and were acromegalic 6 patients had adjuvant therapy after surgery i.e. 3 had octreotide, 1 bromocriptine, 2 had carbergoline, 2 had octriotide and radiotherapy and one died day 10 after surgery after developing IVH and hydrocephalus.(table 6.2 below)

6.2. Growth hormone secreting pituitary adenomas GH levels at diagnosis and six week after operation

GH serum range(ng/ml)	**At diagnosis n(%)**	**6 weeks after op n(%)**
<9-30	0(0)	6(75)
31-50	0(0)	2(25)
51-90	2(25)	0(0)
>91	6(75)	0(0)
Total	**8(100)**	**8(100)**

p-value =0.006

Among 42 patients who had MRI at the time of diagnosis 25(59.5%) had Hardy's classification grade II, 8 patients had grade IV,5 had grade I ,and 4 had grade III (table 7 below) .Thirty five patients were treated surgical and six patients were treated medically and one patient died of pituitary apoplexy while waiting for an operation.

Table7. Radiological classification of pituitary adenomas by Hardy's classification:

Grade	**Number**	**Percentage (%)**
I	5	11.9
II	25	59.5
III	4	9.5
IV	8	19.1
Total	**42**	**100**

Table 8. Major indications for surgery

Groups	Symptoms	Number	Percentage (%)
Pressure effect	Poor vision	16	34.0
	Headache	18	38.4
Secretory	Diabetic	10	21.3
	Nelson syndrome	1	2.1
	Cushing syndrome	1	2.1
	No Response to medical treatment	1	2.1
Total		**47**	**100**

In those 35 patients who had pituitary adenomas and were operated indications for operation in 34(72.4%) were pressure related symptoms and 13(27%) were secretory related effects. Among those who reported pressure related symptoms 16(34%) had poor vision and 18(38.4%) reported to have headache (table 8 above).

Among 35 patients who had surgery 25(71%) had transphenoidal surgery and 5(14.3%) had transcranial route for tumour excision. For those 25 patients who had transphenoidal route 16(64%) had improvement in vision and Among 5 patients who had transcranial tumour excision 4(80%) had improvement in their vision status (p-value <0.061).Two patients one who underwent transphenoidal and another endoscopic transphenoidal surgeries died due to post operative complications(table 9 below) .

Table 9: Surgical approach used in those patients who required surgery and the outcomes

Operations	**Outcome**		**Total**
	Improved	**Not improved**	**n(%)**
	n(%)	**n(%)**	
Transcranial	4(80)	1(20)	5
Transphenoidal	16(64)	9(36)	25
Endoscopic	1(33.3)	2(66.7)	3
Combined transphenoidal+transcranial	1(50)	1(50)	2
Total	**22(62.8)**	**13(37.2)**	**35**

p-value =0.61

Amongst 35 patients who were operated 2(14.3%) had post operative transient CSF leak, and were from transphenoidal group, 5(14.3%) had DI. Also 3 (8.6%) patients had Meningitis and 10(29.4%) had permanent hypopituitarism. Apart from those complications mentioned, also one patient had a post op seizures and other one had Addisson's crisis (table 10 below).

Table10.Distribution of Complication in Relation to surgical approach

	Yes	**No**	**Total**
	n(%)	**n(%)**	**N**
Transcranial	0(0)	5(100)	5
Microscopic Transphenoidal	2(8)	23(92)	25
Endoscopic transphenoidal	0(0)	3(100)	3
Combined(trasnphenoidal and transcranial	0(0)	2(100)	2
Total	2(14.3)	33(85.7)	35
P-value 0.83			
Transcranial	1(20)	4(80)	5
Microscopic Transphenoidal	4(16)	21(84)	25
Endoscopic transphenoidal	0(0)	3(100)	3
Combined (transcranial and microscopic Transphenoidal)	0(0)	2(100)	2
Total	5(14.3)	30(85.7)	35
P-value = 0.79			

Trasncranial	0	5(100)	5
Microscopic Transphenoidal	3(12)	22(88)	25
Endoscopic transphenoidal	0(0)	3(100)	3
Combined(transcranial and microscopic transphenoidal)	0(0)	2(100)	2
Total	3(8.6)	32(91.4)	35

P-value =0.73

Transcranial	0	5	5
Microscopic Transphenoidal	10(40)	15(60)	25
Endoscopic Transphenoidal	0(0)	3(100)	3
Combined (microscopic transphenoidal and transcranial)	0(0)	2(100)	2
Total	10(29.6)	25(71.4)	35

P-value = 0.13

Amongst 35 patients who underwent pituitary tumour excision 12(34.3%) of histology showed Growth hormone releasing Hormone, Prolactin, Gonadotrotopes, TSH and 8(22.9%) had Growth hormone secreting tumour under microscopic classification based on staining, 15(42.9%) were acidophilic, 13(37.1%) were Basophilic and 3 histology were non –specific.(table 11 below)

Table11. Histological distribution of pituitary adenoma operated at IALCH

	Number	**Percentage (%)**
Prolactin secreting Tumour	3	8.6
GH secreting tumour	8	22.9
GH,PRL,LH	6	17.1
Corticotrophe	2	5.7
GHRH,PRL,Gonadotropes,TSH	12	34.3
Thyroid secreting tumour	1	2.8
Bloods clots + Necrotic tissues	1	2.8
Extensive infarction ,no tumour cell	1	2.8
No documentation	1	2.8
Microscopic appearance		
Chromophobes	4	11.4
Acidophil	15	42.9
Basophils	13	37.1
Others	3	8.6

Six patients who had Hardy's grade II had prolactinomas so they were not operated and treated medically (they were treated by endocrinologist and had follow up on both endocrine and neurosurgery clinics).

One patient who had Hardy's and Wilson grade III died of pituitary apoplexy before being operated and died. Out of 5 patients who had transcranial tumor excision 3(60%) had residual tumour, one required reoperation via transphenoidal route, other was lost to follow up, 20 (80%) had small residual.3 patients had endoscopic transphenoidal tumour excision and 2 patient had combined transcranial and transphenoidal surgery.(table 12 below)

Table12.Association between the Tumours grading and surgical approach in pituitary adenoma

Hardy's classification	Cranial Approach n(%)	Transphenoidal Approach n(%)	Endoscopic Endonasal Approach n(%)	Combined Transphenoidal +transcranial approach(n%)	Total n(%)
I	0(0)	5(20)	0(0.0)	0(0)	5(14.3)
II	2(40)	11(44)	2(66.7)	0(0)	15(42.9)
III	3(60)	3(12)	0(0.0)	0(0)	6(17.1)
IV	0(0%)	6(24)	1(33.3)	2(100)	9(25.7)
Total	5(100)	25(100)	3(100)	2(100)	35(100)

p-value= 0.14

Amongst five patients who were operated trans-.cranially had a pterional approach. Two patients had no residual tumour on a MRI done at six month and were followed up, 3(60%) had significant residual tumour and among them 2 patient were re-operated by transphenoidal route, one lost to follow up.

Twenty five patient with pituitary adenoma were operated via transphenoidal route,20% had no residual tumour at 6 month and 80% had residual tumour, 9 had significant residual tumour with symptoms which necessitated reoperation,8 were followed up,5 were subjected to medical therapy (these among those with GH secreting tumours) one was sent for adjuvant stereotactic radiotherapy, other one died day 10 post op in ICU after she developed intraventricular hemorrhage and dropped GCS to 3,CT scan done showed IVH with HDC.

Three patient had endoscopic trans nasal transphenoidal operation, one had no residual tumour at 6month post op MRI,one died post operative day 14 after she developed IVH and HDC and later on developed meningitis after the external ventricular drain insertion and the other one who had residual tumour refused to be re-operated .

Two patients (Hardy's IV) had combined trans-cranial followed by transphenoidal surgery in interval of 2-3 weeks time, 6 month MRI showed residual in one patient whom was advised to have adjuvant radiotherapy and declined (table 13 page 38)

Table13. Association between surgical approach and residual tumour

Route	No residual n(%)	Residual n(%)	Done	Total N
Transcranial	2(40)	3(60)	2-Followed up 2-op transph 1-Lost follow up	5
Transphenoidal	5(20)	20(80)	9- reoperated 8-Followed up 5-Medical Rx 2-Radiotherapy 1-Died post op	25
Endoscopic transphenoidal	1(33.3)	2(66.7)	1-Refused reop 1-died post op	3
Combined	1(50)	1(50)	1-Follow up Refused Radiotherapy	2(100)
Total	**9(25.7)**	**26(74.3)**		**35(100)**

p-value= 0.22

4.2. DISCUSSION

Pituitary tumours are not uncommon, comprising 10-15% primary brain tumours, incidental pituitary tumours are detected in 25 % [34]. Peak incidence is between third and six decade. In this study of 42 patients, mean age was 43 years, ranging from 19 years to 76 years .In this study functional tumours contributed to 27% and non functional tumours 72.4% and this was comparable to Sudhir study [1] whereby functional tumours were 30% and 60% [1]. Sixty seven percent were female and 33% were males, male to female ratio was 1:2 and there was no statistical significance in terms of age and sex (p- value <0.15).These findings are were in agreement with other studies.

In Sudhir study [1] prolactinoma constituted 30% pituitary adenomas and 50 to 60 % of functional pituitary adenomas while in this study it was found that prolactinomas constituted 22% pituitary adenoma and 56% of functional pituitary adenomas seen at IALCH this slightly low value could be explained by the fact that some of the prolactin secreting tumour are referred directly to endocrinologist and they consult a neurosurgeon when patient is clinically and radiological not responding to medical treatment.

Patients with pituitary adenoma may present with signs and symptoms related to mass effects, secretory effects or hypofunction of the pituitary or hypothalamus due to stalk effect. In this study 33% presented with headache and 52.7% with visual disturbances, these included unilateral or bilateral decrease in visual acuity, ranging from mild decrease to complete blindness, others were cranial nerve palsy, 2 patients had acute onset of headache and were diagnosed apoplexy (4.8%) after CT scan and MRI. In literature headache reported to be a common presentation in 33 to 72% o to patient, and visual disturbance seen in up to 65% , apoplexy is in up to 3-17% [9,10,14,23]. The high incidence of pituitary apoplexy could be explained by larger sample sizes in those studied compared to this study. Also 8.8% of patients with prolactinoma presented with amenorrhea and secondary infertility. Among the prolactinoma patients, 6.5% had galactorrhea, one (1.6%) male patient had gynacomastia 5.2% reported to have decreased libido and this is comparable to other studies [14, 23].

GH secreting hormone tumour was seen in 19% of cases, their age at presentation ranged from 19 years to 50 years.GH hyper secretion usually affect almost every organ in the body, this study shows that 25% of patient presented with sleep apnoea, facial pain, excessive sweating and weight gain and Diabetic patients, only one patient had hypertension. Musculoskeletal affectation (frontal bossing, large beefy hands and feet, coarse facial features) were seen in more than 70.3% of acromegalic patient. Also there was a patient with MEN I disease, before presenting with acromegaly he had laboratory the pancreatic tumour. In a study by Mary L. et al, on acromegaly a fascinating pituitary disorder insulin resistance and diabetic mellitus was seen in 25-50 percent [18]. These study findings conform to literatures [3, 6, and 11].

Cushing disease was encountered fairly infrequently in our study population averaging only 4.7%.They presented with disfiguring effects of hypercortisolemia including hyperglycemia, hypertension, hisuitism, supraclavicular pads of fats, hyper pigmentation of the skin and obesity. One patient presented with Nelson syndrome, after having bilateral adrenelectomy at 15 year and two transphenoidal surgeries thereafter.

A rare case of TSH secreting adenoma was seen, she presented with features of secondary hyperthyroidism, it is reported as a rare condition with incidence of 0.5 to 1 % which is almost similar to this study 2.3% [34]

In almost all patients MRI of the brain were done except in two patients, one was a patient diagnosed after presenting with features of supratentorial hydrocephalus. Other patient with Acromegaly had dyspnoea in two occasions when he was doing MRI [14].

Radiological features were classified according to the Hardy Grading classification. Majority of patient 25(59.5%) were at grade II, 8(19.1%) grade IV, 5(11.9%) and 4(9.5%).Two patients with Cushing disease were in grade I. All acromegalic patients their MRI were done with Neuro-navigation which in some cases there were useful intra-operatively. This was clearly shown in David B. study whereby intra-operative neuronavigation was highly effective and safe treatment way compared to MRI without neuronavigation [28].

For those patients who had functional tumours (Prolactinomas, Growth Hormone tumours, ACTH secreting tumour and TSH secreting tumours) serum hormonal and enzymes levels were done. All prolactinomas patients who had serum prolactin level above 100ng/l, dilution test were done to confirm the tests. Four patients (66.6%) out of six had serum prolactin levels between 50000 to1000001ng/l at a time of diagnosis.

For GH secreting tumours , GH level ,IGF-1 levels and OGTT were done .OGTT was done only in two patient which turned to be positive, other six patient presented as known diabetic patient so OGTT were not done,62.5% of GH secreting tumours at time of diagnosis had serum IGF-1 levels above1101ng/ml and 75% had GH levels above 91ng/ml. In the study by Maura A. on clinical use of pre and post surgical evaluation of abnormal GH response in acromegaly, it has been shown that decreased in GH is an indication of complete removal of the tumour[(35)]. On a rare case of TSH secreting tumour patient had high levels of TSH, T3 and T4.

Visual assessment, formal visual field and acuity tests were done by ophthalmologists preoperatively, and some were done at referring hospital. Patient was asked if she felt any improvement post operatively, no formal assessments done by ophthalmologist.

Surgery is the mainstay of treatment of most of pituitary adenomas, except prolactinomas. In this study 71% of patient who had indications for surgery were treated with transphenoidal surgery,14.3% had transcranial, 8.6 % Endoscopic transphenoidal and 5.7% had combined transcranial and transphenoidal. In Shudirs study total tumour removal via transphenoidal route is achieved in 38%[(1)], in this study 20% of patient who had transphenoidal surgery had no residual tumour in an MRI done in 4 to 6 month post operative period, this is slightly low, could be explained by small number of cases. Also 16% of patient who had transphenoidal surgery reported improvement in their vision post operative. In other 28 % of patient they had no improvement post operative and majority of them were those who had either completely blind in one or both eye at the time of diagnosis.

There was significant residual (80%) of patient who had transphenoidal approach,9 had repeated operation,8 were followed up and 5 cases were subjected to medical treatment(GH secreting tumours) ,one sent to stereotactic radiotherapy and one died of post complication as said early.

Out of five cases who had pterional trans-cranial approach 4 (80%) improved in their vision post operative 3 patients (60%) had residual tumour which necessitated them to have a transphenoidal surgery. During study period Endoscopic transphenoidal was introduced and 3cases were done, result were no residual tumour in one patient, small residual on second patient and one died post operative due to procedure complications. This was small data to compare with literature in which complete tumour excision in up to 79% [14]. Two patients had both transcranial and transphenoidal surgeries. Although transcranial route appears to have high success in tumour removal but patients were few compared with transphenoidal approach to say one was superior to other. Also this study found that there was no statistical significance between the surgical treatment modality and good outcomes (p- value <0.06).

Complications documented were 14.3% had post operative CSF leak, 14.3% had permanent DI among patients who had transphenoidal surgery, overall 8.6% had Meningitis (all from transphenoidal group), 29.6% had permanent hypopituitarism, two patient had pituitary apoplexy one died before operation, there was no statistical significance as far as complication was concern in all four surgical treatment modalities And this study findings are on high side compared to other literatures ([1,27].

Five patient who had prolactinomas were treated medically with bromocriptine and at three to six month and above 50% had significant declining of serum prolactin levels between 2001 to 3000ng/ml and also MRI showed a significant reduction in tumour size and this good response to medical treatment was low compared to other studies (90%) [23] This could be due to small number of patients, and in this study response treatment was assessed at 6month [3, 23]. One patient had deterioration of vision during medical treatment and was operated and augmented with medical therapy post operative.

Another patient had bromocriptine related psychosis and was changed to carbergoline, it was also found that medical treatment had rapid and was better treatment option in

prolactinomas and strong statistical significant (p- value <0.04).This is in support with James K study on contemporary management of prolactinomas whereby 90% responded well to medical treatment but in some patients long term follow up was required [23].

All patient who had GH secreting tumors,75% of patient had significant decline of both GH and IGF-1 which are good indicator of success of surgery, but majority did not have low GH level to suggest biochemical cure and were subjected to either octriotides or somatostatin as adjuvant therapy however there was statistical significance (P-value < 0.006). These results are in parallel with other literatures [3, 7, 8].

Cushing disease patient were also subjected to medical treatment post operative ,ketoconazole was used by both patient but on other hand , a patient who had Nelson syndrome he was changed to Carbergoline due side effects. Patient with TSH tumour was also subjected to octriotides after surgery and responded well.

Three patients were subjected to adjuvant radiotherapy that also developed hypopituitarism. It is documented that recurrence rate is 9 to 19% on patient who had complete tumour removal in a period of 5 to 9 years [21, 22] .This study because o short study period didn't look at the recurrence of pituitary adenoma. However in Carin M study on follow up study with CT and clinical evaluation a 5 to 10year after pituitary adenoma surgery and radiotherapy out of 19 cases 4 recurrences where revealed by a CT scan [22].

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The clinical presentation, mode of treatment of pituitary adenoma patients at IALCH are similar to those published from other institutions. As it was clearly seen transphenoidal surgery was a preferred route by the surgeon in most of the case compared to transcranial route [(1)] however in this study the numbers of cases were small to make a conclusion that one was better than the other.

In this study it was found that late presentation to patients with visual insufficient is associated with poor post operative visual gain.

5.2 Recommendation

1. Primary health education needed to the community on early signs and symptoms o the disease.

2. Majority of patient who had transphenoidal surgery patients were re-operated, it was not very clearly whether they developed symptoms or based on MRI findings, it important that criteria for reoperation should be clearly known.

3. Although IALCH is a paperless hospital, there is a need to improve record keeping. The detailed admission notes, management during and after admission need to be documented properly.

8.3.Limitations of the study

Poor record keeping was a major limitation on study leading to difficulties in assessing some of the parameter in the study.

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Appendix 1

DATA ABSTRACTION FORM

Title; Treatment Modalities and Outcomes of patient with Pituitary adenoma at Inkosi Albert Luthuli Central Hospital at Kwazulu Natal Province

PART I: DEMOGRAPHIC INFORMATION

1.DAF No:_____

2.Patient reg No_____

3.Gender 2.Female 2.Female

4 Age(Year)_____

6.Education level

I.Informal

II.Primary/secondary

III.Higheducation

7.Occupation

I.Peasant

II.Employed

III.Unemployed

IV.Petty trader

V.other_____

8.Residence_____

PART II.GENERAL SYMPTOMS

1.Headache		2.No	2.No
If yes Duration (in Month)			
2.Poor vision		2.No	2.No
Duration (in Month)			
3.Female	I Hx of Amenorrhea	2.No	2.No
	II Hx of Galactorrhea		2.No
	III.Hx of decreased libido	2.No	2.No
4.Male	I.Hx of Impotence	2.No	2.No
	II.Hx of decreased libido	2.No	2.No

PART III.GROWTH HORMONE SECRETING TUMORS

1.Hands enlargement	2.No	2.No
2.Feet enlargement	2.No	2.No
3.Facial pain	2.No	2.No
4.Joint pain	2.No	2.No
5.sleep apnoea	2.No	2.No
6.Excessive sweating	2.No	2.No
7.Skin tag	2.No	2.No
8.Frontal bossing	2.No	2.No
9.Coarse facial features	2.No	2.No

10.Increased spacing between toes and feet	2.No	2.No
11.Large beefy hands and feet	2.No	2.No
12Features of spinal stenosis	2.N0	2.No
13.features of Spinal stenosis	2.No	2.No
14.peripheral neuropathy	2.No	2.No
15.Cardiac arrhythmias	2.No	2.No
16.Skin tags	2.No	2.No
PART IV CUSHING SYNDROME		
1.Weight gain	2.No	2.No
2.Fatique	2.No	2.No
Difficulty in Sleeping	2.No	2.No
4.Irritability	2.No	2.No
5.Depression	2.No	2.No
6.Memory loss	2.No	2.No
7.Difficulty in concentrating	2.No	2.No
8.Bone fractures	2.No	2.No
9.Muscles weakness	2.No	2.No
10.Glucose Intolerance	2.No	2.No
11.Hypertension	2.No	2.No
12.Facial plothera	2.No	2.No
13.Supraclavicular fat deposition	2.No	2.No

14.osterior fat deposition	2.No	2.No
15.Acanthosis nigricans(acne)	2.No	2.No
16.Hirsuitism	2.No	2.No
17.Violaceous stria	2.No	2.No
18.Muscle wasting in upper arm and thigh	2.No	2.No
PART V HYPOGONADISM		
1.Diminished beards and body hair	2.No	2.No
2.Small testes	2.No	2.No
3.Fine wrinkling of the face	2.No	2.No

PART VI RADIOLOGICAL FINDINGS		Follow up	MRI(Tumor)
Hardy's Classification	I		
	II		
	III		
	IV		

PART VII ENDOCRINE PROFILE AT DIAGNOSIS

1.PRL.....

2. Cortisol.....

3.TSH.....

4.T3.....

5.T4.....

6.GH.....

7.IGF-1.....

8.LH.....

9.FSH.....

10.Estrogen.....

11.Ostradial.....

12.Testosterone .....

13.Stimulation Tests a.OGTT Positve/nega b.Dexamethasone suppression test- po

PART VIII TREATMENT

1.MEDICAL TREATMENT(For Prolactinomas)-

a. Drug used _____

Duration in Month_____

2.SURGICAL TREATMENT

INDICATIONS MENTION:

1.....

2.....

I.TRANSPHENOIDAL

II.PTERIONAL

3.SURGICAL COMPLICATION

I.CSF FISTULA DURA

II.DI DURA

III.WORSENING OF VISION DURA

IV.Hypopituitarism DURA

V.Others

PART IX FIRST WEEK AND FIRST FOLLOW UP ENDOCRINE PROFILE

	At 6
1.PRL	.....
2.Cortisol	.....
3.TSH	.....
4.T3	.....
5.T4	.....
6.GH	.....
7.IGF-1	.....
8.LH	.....
9.FSH	.....
10.Testesterone	.....

PART X ADJUVANT THERAPY

1.RADIOTHERAPY yes/No

2.CHEMOTHERAPY Yes/No

PART XI- Residual yes / No

PART XII- REOPARATIONS Yes / No

PART XIII FOLLOW UP MRI at 3 to 6month 6 30

PART XIV

PITUITARY APOPLEX Yes/No

Appendix 2

Hardys Classification of pituitary tumours (MRI used)

Grade I: Microadenomas (<1cm) without Sellar expansion or invasion

Grade II: Macroadenomas (>1cm) and may extend above the sellar, no invasion of the sellar tursica

Grade III:-Macroadenomas with localized invasion

- Enlargement of the Sellar floor

Grade IV: Diffused destruction of Sellar floor

They may have suprasellar and parasellar extension

A) Extension into Suprasellar cisterns only

B) Extension to recesses of the third ventricle

C) Extension to involve the whole third ventricles

D) Involvement of Carvenous sinus

Appendix 3

Ethical clearance.

UNIVERSITY OF
KWAZULU-NATAL

3rd February, 2012

Dr MC Mazoko
Neurosurgery Department
IALCH

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED ''TREATMENT MODALITIES AND OUTCOMES OF PATIENTS WITH PITUITARY ADENOMA AT INKOSI ALBERT LUTHULI CENTRAL HOSPITAL AT KWAZULU NATAL PROVINCE SOUTH AFRICA JAN 2007 TO DECEMBER 2012''

Reference made to the above heading.

I am pleased to inform you that, the Chairman on behalf of the Ethical clearance board approved ethical clearance for above mentioned study.

By the way of this letter, Ethical clearance is granted to proceed with planned studies.

I wish you all the best.

Dr E. M .Kiratu
Head of Neurosurgery department