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GUIDELINES FOR PITUITARY ADENOMAS

Pituitary Adenomas: Tailoring Management to Resource-Limited Settings in LMICs

Ather Enam¹, Najmul Islam²

Managing functional and nonfunctional pituitary adenomas presents unique challenges in low- and middle-income countries (LMICs). These medical and socio-economic challenges require a tailored approach to diagnosis and treatment. We, the editors of this supplement, are proud to present this JPMA supplement, which modifies existing guidelines to better suit the realities of LMICs, aiming to provide practical, resource-conscious strategies for managing pituitary adenomas.

Pituitary adenomas, accounting for approximately 10-15% of all intracranial tumours, can lead to significant health issues due to their location at the base of the brain and their potential to disrupt hormonal balance and neurological function. The impact of these tumours is compounded in LMICs by numerous public health issues. These include the lack of health insurance and inadequate government support for medical expenses, leading to out-of-pocket payments that many patients cannot afford. Furthermore, patients often travel long distances to seek medical advice, and the cost of diagnostic tests can be prohibitively expensive given these regions' low GDP per capita. The risk of catastrophic medical expenses pushing patients beyond the poverty line is a pressing concern that needs urgent attention.

While guidelines for managing pituitary adenomas exist globally, they cannot be blindly followed in LMICs due to these resource limitations. Hence, this supplement aims to produce guidelines pertinent and appropriate to the local context, ensuring that care is effective and feasible within the constraints faced by healthcare providers and patients in LMICs.

Accurate and early diagnosis is the cornerstone of effective pituitary adenoma management. However, in resource-limited settings, the approach must be

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pragmatic. A thorough clinical evaluation can be performed with minimal resources and hormonal assessments should be prioritized based on a clinical presentation to reduce costs. Imaging studies, particularly MRI, are critical but should be used judiciously, with efforts made to access subsidized services or community-based programmes to ease financial burdens on patients.

Treatment strategies need to balance efficacy with cost-effectiveness. For functional adenomas, the guidelines advocate using the most cost-effective pharmacological agents available, considering the local availability of drugs such as dopamine agonists, somatostatin analogues, and cortisol-lowering medications. The cost of treatment becomes a crucial factor in LMICs. Sometimes, surgery may be a more cost-effective option than expensive medications to control hormones. Although often necessary, surgical resection must be approached with a focus on optimizing available resources. The guidelines recommend the use of transsphenoidal surgery as the gold standard due to its minimally invasive nature and shorter recovery times, which are crucial in settings with limited inpatient facilities. Efforts should be made to train local surgeons in these techniques and to establish regional centers of excellence to minimize the need for long-distance travel.

Long-term follow-up is essential but must be realistic in resource-limited settings. The guidelines suggest a structured follow-up protocol that leverages telemedicine and community health workers to monitor patients remotely, reducing the need for frequent hospital visits. Hormonal evaluations and imaging should be performed based on clinical indications rather than routine schedules to minimize unnecessary costs. A patient-centered approach is crucial for maintaining treatment adherence and monitoring for potential recurrences or complications. Establishing support networks and providing patient education can help improve long-term outcomes.

This supplement represents a significant step towards addressing the unique challenges of managing pituitary

adenomas in LMICs. By providing tailored guidelines, we aim to improve diagnostic accuracy, optimize treatment outcomes, and reduce the financial burden on patients, ultimately enhancing the quality of life for those affected by these tumours.

We would like to express our sincere gratitude to all contributors who generously shared their expertise, and to the JPMA for their unwavering commitment to improving healthcare standards. Special thanks to Ms. Farah Khalid, Assistant Managing Editor at the Journal of Pakistan Endocrine Society (JPES), for her invaluable assistance throughout the manuscript formatting and submission process. We also extend our heartfelt appreciation to Mr. Atif Jamal, IT Support at the Pakistan

Endocrine Society, and Ms. Sonia Ahmed, Social Media Specialist at the Pakistan Society of Neuro-Oncology, for their dedicated efforts in designing the cover.

As we move forward, we encourage ongoing research and collaboration to further refine and update these guidelines, ensuring that they remain aligned with the latest advancements in medical science while being grounded in the realities of our local context. These guidelines are not final. This is a humble effort, and we will eagerly modify them based on the principles that guided us in writing these guidelines. We welcome criticism, suggestions, and recommendations for modifications to ensure that our next supplement is even more robust and appropriate.

Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Non-functioning Pituitary Adenoma

Komal Naeem¹, Mohammad Hamza Bajwa², Fatima Mustansir³, Zaira Khalid⁴, Maliha Taufiq⁵, Shahzad Shamim⁶, Asif Bashir⁷, Tariq Khan⁸, Ehsan Bari⁹, Najmul-Islam¹⁰, Kamran Saeed¹¹, Syed Ather Enam¹²

Abstract

Pituitary adenomas comprise approximately 10 to 20% of intracranial tumours. From an endocrinologic perspective, pituitary tumours can be broadly classified as functional pituitary adenomas (FPAs) and non-functional pituitary adenomas (NFPAs). All pituitary tumours that are not associated with a clinical hypersecretory state are categorized as NFPAs, including, null cell adenomas and silent adenomas. NFPAs are benign adenohypophyseal tumours that do not present with clinical evidence of hormonal hypersecretion. NFPAs constitute one-third of all pituitary tumours. They usually come to medical attention as a result of mass effect symptoms, while some may present with hypopituitarism or hyperprolactinaemia. Occasionally, they may be diagnosed incidentally through imaging studies performed for other reasons. A "watch and wait" option is reasonable for microadenomas and asymptomatic patients while surgical resection is indicated for symptomatic patients. The use of radiotherapy and medical therapies as a first-line treatment modality is debated and may be reserved for cases of residual tumours, progressive tumour growth, or tumours with aggressive features. The Pakistan Pituitary Adenoma Guidelines Committee (PPAGC), comprising neurosurgeons, endocrinologists, oncologists, and radiation oncologists was established to create management guidelines for both functioning and non-

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functioning pituitary adenomas, specifically for use in low- and middle- income countries. This paper presents the guidelines put forth by this committee of experts.

Summary of recommendations

Recommendation 1.1: All NFPA patients should be inquired about consanguinity during comprehensive clinical assessment.

Recommendation 1.2: An urgent neurosurgery referral is warranted for the patients presenting with pituitary apoplexy.

Recommendation 2.1: All MRIs should be done according to the pituitary protocol.

Recommendation 2.2: All patients should undergo biochemical evaluation for hormone hyper- and hypo-secretion.

Recommendation 2.3: A comprehensive ophthalmologic evaluation is mandated for lesions compressing/abutting optic apparatus on imaging.

Recommendation 3.1: A multi-disciplinary comprehensive assessment, treatment planning, and follow-up for each patient is recommended.

Recommendation 3.2: Observation is an appropriate treatment modality for patients with stable asymptomatic microadenomas.

Recommendation 3.3: Surgical resection is a standard treatment for symptomatic NFPAs.

Recommendation 3.4: A thorough hormonal assessment and for preoperative clearance by an endocrinologist is warranted for all patients.

Recommendation 3.5: Surgical resection is recommended for adenomas discovered during pregnancy presenting with visual field deficit.

Recommendation 3.6: It is important to consider patient demographics, comorbidities, and medication history

while planning for surgery.

Recommendation 3.7: All patients taking long-acting anti-clotting medications, preoperatively, should be switched to short-acting anti-clotting agents, followed by their resumption at an appropriate interval.

Recommendation 3.8: The decision between the trans-sphenoidal vs trans-cranial approach should be based on preoperative radiological parameters.

Recommendation 3.9: Comprehensive histopathologic and molecular analysis is performed for NFPA tumour samples.

Recommendation 3.10: Serum sodium levels and urine output monitoring in the immediate postoperative period is crucial.

Recommendation 3.11: There are limited indications for the use of Radiotherapy (RT) as a first-line treatment.

Recommendation 3.12: Sizeable residual tumours, following surgery, should be treated with the radiotherapy.

Recommendation 3.13: A radiation dose of 12 Gy for single-dose radiotherapy and 45-54 Gy for fractionated Stereotactic Radiosurgery (SRS) is recommended.

Recommendation 3.14: There should be a safe distance of 2 mm, at least, from the optic chiasm while considering RT for residual tumour measuring ≤ 3 cm.

Recommendation 3.15: Medical therapy for recurrent aggressive NFPA, not responding to other interventions, should be considered. The decision is at the oncologist's discretion.

Recommendation 4.1: A comprehensive history, physical examination, biochemical evaluation, and visual assessment are required for all patients presenting with an incidentaloma.

Recommendation 4.2: Management of a micro-incidentaloma is similar to that of an asymptomatic microadenoma (recommendation 3.2).

Recommendation 4.3: Pituitary protocol MRI should be done for all macro-incidentaloma discovered on a different imaging modality.

Recommendation 4.4: For macro-incidentaloma at >5 mm distance from chiasm MRI and biochemical evaluation should be done at the one-year follow-up.

Recommendation 4.5: Surgery should be considered for the macro-incidentaloma close to the optic chiasm (<5

mm distance).

Recommendation 4.6: Surgical resection is indicated when the tumor compresses the optic apparatus, results in pituitary apoplexy, or causes hypersecretion (except prolactinomas).

Recommendation 5.1: Postoperative biochemical assessment is recommended every 3 months for one year followed by an indefinite 6-to-12-month follow-up, especially in instances of preoperative deficiency.

Recommendation 5.2: Close imaging follow-up for all NFPA cases is recommended: first scan at 3-to-6-month follow-up, second at 1 year, then annually for 5 years, followed by at 7-, 10-, and 15-year intervals.

Recommendation 5.3: All NFPA patients should have close ophthalmologic follow-up(s). In case of deficit, assessment should be done at the 3-month follow-up and then repeated every 6 months.

Recommendation 5.4: Teleconsultation is a preferred mode of follow-up when the probability of patients' loss-to-follow-up is high.

Recommendation 5.5: Post-treatment, patient counselling should be done in detail including explanations of warning signs for disease progression/recurrence.

Recommendation 5.6: Surveillance for small intrasellar residual tumours is recommended. Annual serial imaging for 5 years followed by every 2-3 years.

Recommendation 5.7: Adjuvant radiotherapy ensures good disease control.

Recommendation 5.8: A multidisciplinary decision should be made when considering surgical resection of symptomatic residual tumours.

Recommendation 5.9: Both, a repeat surgical resection or RT, for the management of recurrent tumours may be considered.

Introduction

Pituitary adenomas (PAs) are intracranial neoplasms arising from the anterior pituitary gland (adenohypophysis). They make up 15% of primary brain tumours and 25% of benign brain tumours. Its frequency ranges from 3 to 94 cases per 100,000 people. They are the third most common brain tumours behind gliomas and meningiomas. Their prevalence is the highest between the fourth and seventh decade of life. Pituitary adenomas have a propensity to occur in women however, they are more commonly seen in men aged 55-85. Even

though the majority of pituitary adenomas arise sporadically, some may be associated with certain hereditary endocrine syndromes such as multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4), and familial isolated pituitary adenomas (FIPAs).¹

Pituitary adenomas can be broadly classified as functioning pituitary adenomas (FPAs) and non-functioning pituitary adenomas (NFPAs). FPAs liberate physiologic hormones in pathologically excess quantities, which manifests as metabolic anomalies while NFPAs are hormonally inactive and cause compressive symptoms. Studies have shown that FPAs are more common in younger patients while NFPAs occur more commonly in older adults.^{2, 3}

Non-Functioning Pituitary Adenoma: NFPAs are the second most common pituitary adenomas following prolactinomas and are the most common type of macro-adenomas. They have an estimated incidence of 7 to 41.3 cases per 100,000 people. NFPAs are mostly diagnosed after the age of 40 years, with women presenting earlier than men.⁴

At least 60% of NFPAs are macro-adenomas (>10 mm in diameter) and usually present with mass effect.⁵ Their diagnosis may also be made due to the compression of nearby vital structures which can lead to the development of anterior hormonal deficiencies or hyperprolactinaemia and vision loss.⁶ An increasing number of NFPAs are incidentally diagnosed during radiological imaging investigations performed for unrelated purposes – known as pituitary incidentalomas.⁷

NFPAs can be further classified according to their pituitary hormone and transcription factor profile.

1. Silent PAs – these tumours express one or more anterior pituitary hormones or their transcription factors with immunohistochemistry but the levels of hormones are not clinically significant.
2. Null cell adenoma - exceptionally rare primary adenohypophyseal tumours that show immunonegativity for all adenohypophyseal hormones and a lack of cell-type specific transcription factors.^{3,7,8}

Methodology

1. Formation of Working Groups: After recognition of the current landscape regarding gaps in the management of pituitary adenomas in Pakistan, a collaborative committee, the Pakistan Pituitary Adenoma Guidelines Committee (PPAGC) was convened consisting of members from the Pakistan Endocrine Society (PES) and

the Pakistan Society of Neuro-oncology (PASNO). This multidisciplinary panel of experts consisted of stakeholders representing various fields including neurosurgery, endocrinology, and radiation oncology. The committee was chaired by the presidents of PASNO and PES, who further appointed members into two working groups: non-functioning pituitary adenomas (NFPAs) and functioning pituitary adenomas (FPAs). Each group consisted of consultants along with junior researchers who would assist in evidence collection and compilation of recommendations.

After multiple meetings and discussions within the two working groups, draft papers were submitted to the committee from each group. These drafts were reviewed by senior experts in the field. These guidelines were revised according to their feedback and final papers were presented at a general meeting of the PPAGC. All comments and suggestions were considered and added by the respective working groups.

2. Delphi Exercise for Prioritization of Topics and Ratification of Recommendations: Junior researchers collected evidence through a systematic database search to identify best-practice guidelines for the management of pituitary adenomas. The databases used were PubMed, Wiley Cochrane Library, and Web of Science. After a subjective assessment of guideline papers and recommendations, data was extracted regarding recommendations according to respective specialties i.e. neurosurgery, radiation oncology, endocrinology, and oncology. These guidelines were further discussed with experts from each respective working group. The quality of evidence was based on expert opinion. Recommendations were made regarding the practical application of these best-practice guidelines to LMIC settings, such as in Pakistan. Local and regional published articles on the management of pituitary adenomas were also reviewed.

Recommendations

Clinical Presentation and Evaluation

Recommendation 1.1: All NFPA patients should be inquired about consanguinity during comprehensive clinical assessment

Pakistan has a high prevalence of consanguineous unions.⁹ When a patient comes to the clinic, it is important to inquire about consanguinity to rule in/out genetic syndromes while taking a detailed history and performing a comprehensive neurological exam. At the time of initial presentation, 85% of hormonally inactive tumours show symptoms of pituitary insufficiency.¹⁰⁻¹²

Therefore, it is also critical to evaluate the symptoms of pituitary insufficiency and hypersecretion, including but not limited to, intolerance to cold, menstrual irregularities, infertility, erectile dysfunctions, issues with lactation, changes in weight, mood, skin, and appetite, low blood pressure, acne, excessive hair growth, hair loss, and weak/brittle bones.^{12, 13} (Fig. 01)

1.1.1. Mass Effect symptoms – headaches, visual field deficits: NFPA is a slow-growing tumour and often presents with the symptoms of mass effect. The pituitary gland is situated in close proximity to the optic chiasm and any space-occupying lesion (SOL) can lead to a visual deficit. This warrants comprehensive testing as visual field defect is an indication of surgical resection.

SOL leads to increased intracranial pressure (ICP) which may present as disabling headaches. Although headache is a prevalent symptom, its causal effect with adenoma has not been established and it does not serve as an indicator for intervention. Headaches should always be evaluated with the complete clinical presentation of the patient and other causes need to be ruled out first.^{3,12,13}

1.1.2. Cranial nerve palsy: Patients may present with isolated oculomotor nerve (cranial nerve [CN] III) palsy. An isolated palsy is not an absolute indication of surgery. A decision regarding invasive intervention is at the physician's discretion.¹³

Recommendation 1.2: An urgent neurosurgery referral is warranted for the patients presenting with pituitary apoplexy

Pituitary apoplexy is a dreaded complication of NFPA and warrants an immediate evaluation. Patients usually present with severe headaches and vision impairment due to chiasm or oculomotor nerve compression.^{3,5} Patients with macroadenomas close to the optic chiasm should be counselled regarding the risk of apoplexy and its consequences. In acute-phase apoplexy (within the first few hours after the onset of symptoms), Computed Tomography (CT) scans can be highly sensitive in detecting haemorrhage as compared to MRI scans. (Fig. 02) However, after this time, MRI is the preferred imaging technique. As an emergent condition, the management of apoplexy requires involvement from neurosurgery, neuroradiology, endocrinology, and ophthalmology specialty services.¹³ It is advised that patients be admitted to centres with adequate emergency neurosurgery care, if possible. (Fig. 01)

In most circumstances, hormonal deficiencies are present requiring immediate hydrocortisone replacement – patients in the emergency room can be started on

intravenous medications and shifted to oral formulations once stabilized. Surgery is indicated in case of altered mental status or rapidly worsening visual defects. Cranial nerve palsies may also be considered for urgent intervention. (Figs. 01 and 02) If the current hospital is unable to provide surgical care, the patient should be immediately referred to a nearby centre with such capabilities and surgery should be performed as soon as possible. Particularly within LMICs, a dedicated pituitary tumour surgeon is not necessary, but it is preferable to have an experienced surgeon with considerable experience in pituitary surgery.

In cases where there are contraindications to urgent surgery (little to no benefit after intervention) or the patient's visual loss and deficits are long-standing, conservative management can be considered with high-dose glucocorticoids with clinical and ophthalmologic surveillance. These are temporary measures to delay surgery for a few days to ensure optimization of the patient's clinical condition before intervention.¹³ (Fig. 01)

Diagnostic Workup

Recommendation 2.1: All MRIs should be done according to the pituitary protocol

Recommended MRI protocol is as follows:^{12,13} (Fig. 01)

- A minimum field strength of 1.5 Tesla
- High matrix, thin (≤ 3 mm) slices, coronal and sagittal T1-weighted sequences, with and without contrast (Gadolinium)
- Coronal T-2 weighted sequences
- Coronal three-dimensional volumetric assessment with reconstruction, otherwise very thin slices with a reference plane are needed.

It is important to identify haemorrhage/necrosis and extension of the lesion along with the normal anatomy (pituitary stalk, posterior lobe, and remaining healthy pituitary parenchyma).¹³ A high-resolution pituitary protocol MRI is considered the gold standard (level II). It can be accompanied by a CT scan (level III). Cavernous sinus invasion and tumour vascularity can be assessed on perfusion MR and Gradient echo. Literature does not support the utility of MR spectroscopy, Positron emission tomography (PET), or Single-photon emission computed tomography (SPECT).⁵

Recommendation 2.2: All patients should undergo biochemical evaluation for hormone hyper- and hypo-secretion

Hormonal workup is critical for the accurate diagnosis of

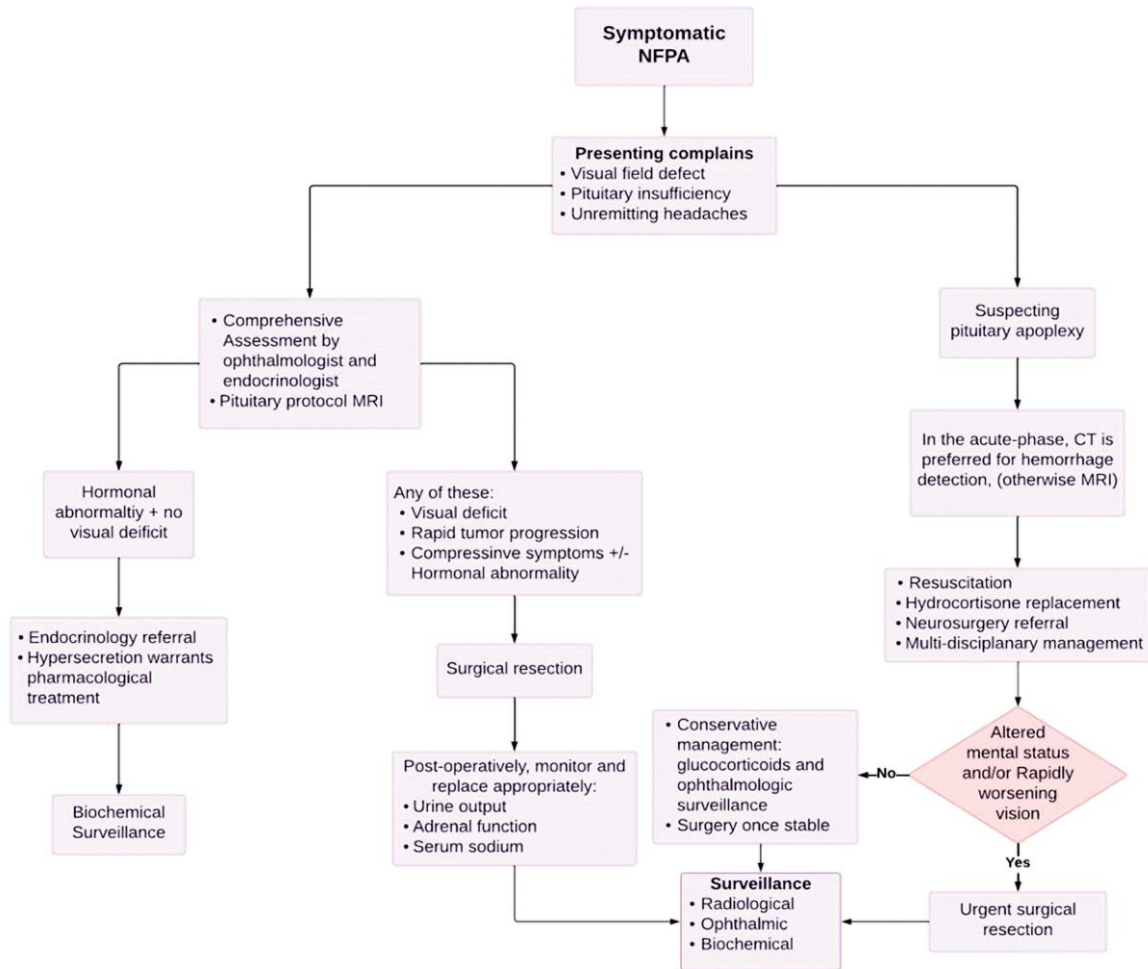


Figure-1: Algorithm for management of symptomatic Non-Functioning Pituitary Adenoma (NFPA)
(Abbreviations: CT: Computed Tomography; MRI: Magnetic Resonance Imaging)

pituitary adenomas and affects management. The treatment paradigm for hormone hypersecretion is very different from that of pituitary insufficiency. At the initial presentation, around 60-85% of macro-NFPAs present with at least one pituitary hormone deficiency.^{12,13} The most common deficiency is of gonadotroph (>80%), followed by somatotroph, thyrotroph, and corticotroph deficiencies.^{3,12,13} These deficiencies can be life-threatening, making comprehensive hormonal analysis an important diagnostic work-up for NFPA. Somatotroph deficiency screening is not mandatory.¹³

Hyperprolactinaemia may occur due to the stalk effect in 38.7% of the NFPA cases. The stalk effect is defined as the interruption in tonic inhibition by dopamine (secreted from the hypothalamus) secondary to the tumour compressing the pituitary stalk, which leads to the increased secretion of Prolactin (PRL)^{5,14}

Recommendation 2.3: A comprehensive ophthalmologic evaluation is mandated for lesions compressing/abutting optic apparatus on imaging

Comprehensive evaluations should be carried out by the ophthalmologist:

2.3.1. Optic Nerve (CN II) exam: Either Visual acuity (VA) measurement or visual field exam (VF), central static and peripheral kinetic is indicated. Optical coherence tomography (OCT) can be an adjunct but does not contribute to prognosis evaluation. Fundus and anterior segment examination is also recommended.

2.3.2. Oculomotor nerve (CN III) exam: the patient should be inquired about diplopia during history along with a nine-gaze directions exam. Lancaster or orthoptic exam can also be performed.

These visual examinations are necessary at radiological

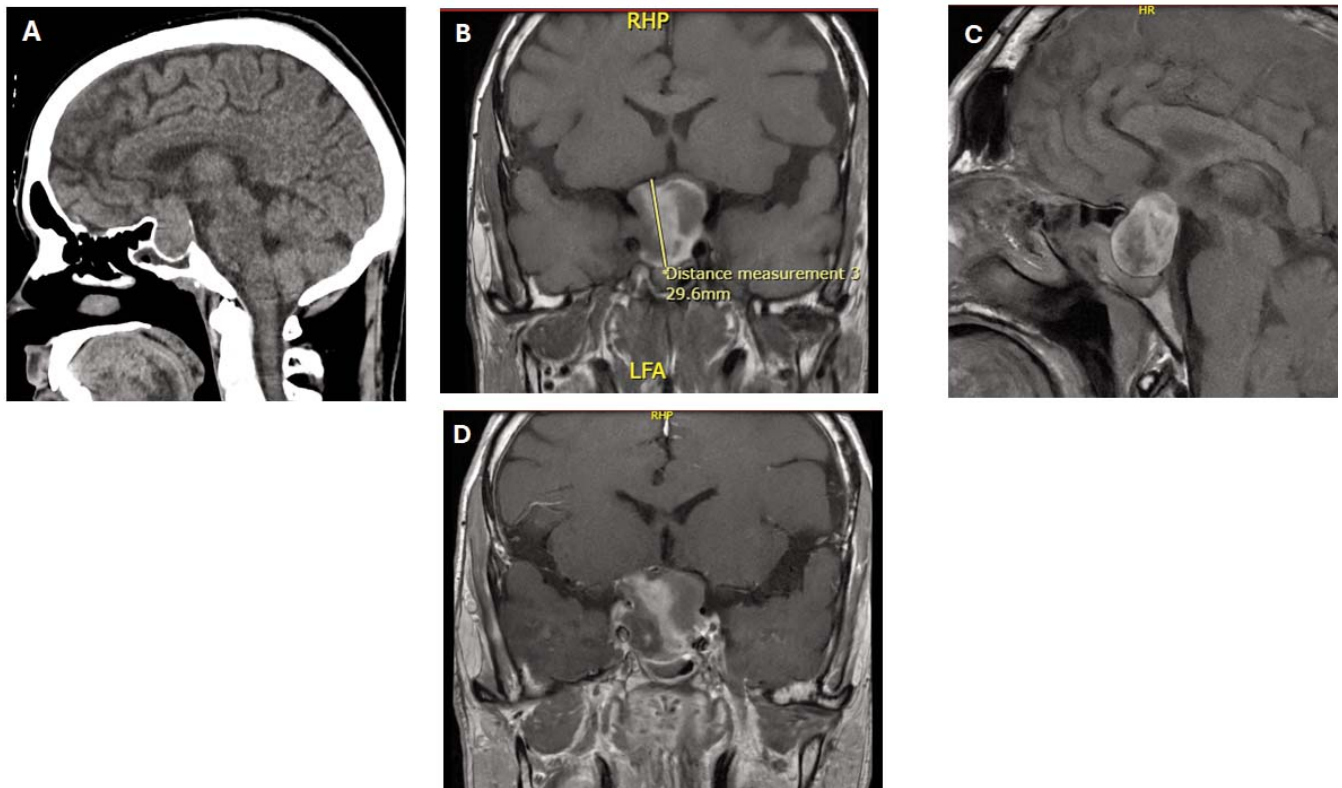


Figure-2: Pituitary apoplexy. 60-year-old male presented to the emergency department with sudden loss of vision and headache. Patient was diagnosed with Pituitary Apoplexy (A) CT redemonstrating large heterogenous sellar mass compressing sphenoid sinus. Multiple hypodense regions, signifying necrosis, can also be seen. Pituitary Protocol MRI (B) T1-weighted coronal view of MRI demonstrating a large heterogenous sellar mass, measuring 29.6 mm, with supra-sellar extension, right-sided cavernous sinus invasion, and optic chiasm compression (C) T1-weighted sagittal MRI showing large heterogenous mass. Note small field of view (FOV). (D) Hyperintensity can be seen at the periphery of the lesion without any significant post contrast enhancement, suggestive of hemorrhage

diagnosis, within 3 months of surgery, and before radiation therapy (RT). When the lesion is abutting or compressing the optic chiasm follow-ups should occur at regular intervals for visual involvement, progression, and before scheduled RT.^{12,13}

Management

Recommendation 3.1. A multi-disciplinary comprehensive assessment, treatment planning, and follow-up for each patient is recommended

It is important to have an endocrinologist, ophthalmologist, and neurosurgeon involved in the care of patients with NFPA. If the decision for surgery is made, it is equally important to follow up with the endocrinologist and ophthalmologist (in case of visual field defects). Care needs to be established preoperatively and should be re-emphasized in the postoperative period.¹² (Fig. 01)

Not all tumours warrant surgical resection as first-line treatment, especially those presenting with

hypersecretion. For lesions with hypersecretion (hyperprolactinaemia, acromegaly or Cushing's syndrome) evaluation by an endocrinologist is recommended. Treatment with appropriate pharmacologic agents should be prescribed, as per the guidelines.^{12,13} Therefore, it is important to perform a comprehensive hormonal assay for accurate diagnosis.

Observation

Recommendation 3.2. Observation is an appropriate treatment modality for patients with stable asymptomatic microadenomas.

3.2.1. Tumours <5 mm do not require additional imaging unless there are any new symptoms

Observation is an appropriate choice in cases of tumours of small size (<5 mm), symptomless, and without any endocrinological dysfunction. Patients should be counselled regarding return precautions.^{12,15}

3.2.2. A minimum follow-up of two years for tumours

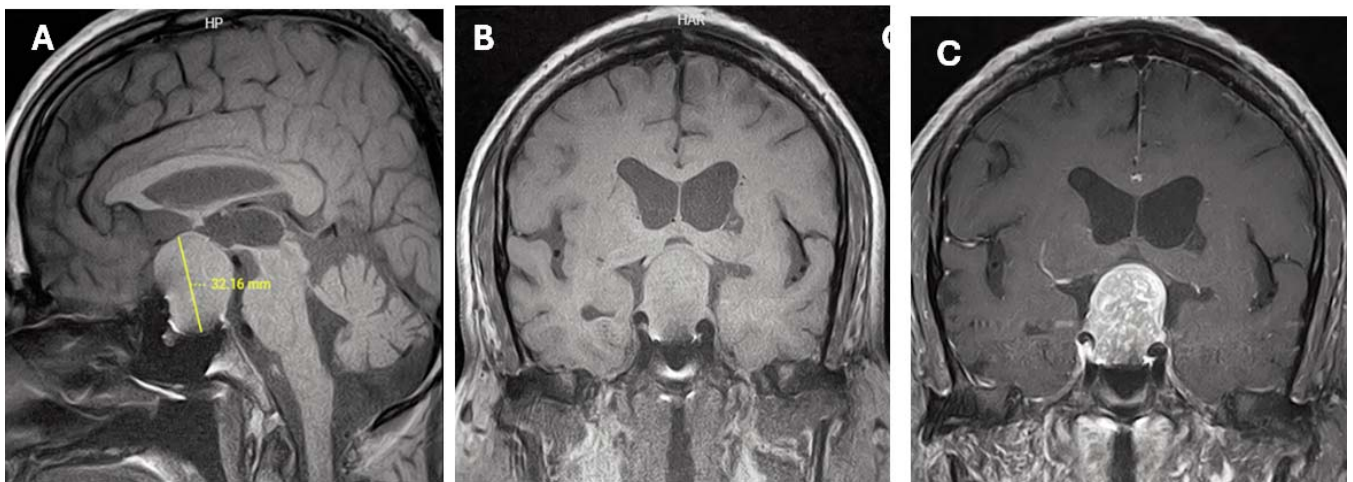


Figure-3: Pituitary macroadenoma. 52-year-old male presented with mild vision impairment, gait abnormality, and headache. Patient was diagnosed with pituitary macroadenoma. Based on clinical symptoms and radiological evidence of chiasm compression decision for trans-sphenoidal resection was made. Post-operatively, patient recovered well and reported symptoms resolution. Pituitary Protocol MRI (A) T1-weighted sagittal view of MRI showing a large sellar lesion, measuring 32 mm in craniocaudal dimension, with supra-sellar extension. (B) Coronal T1 weighted MRI re-demonstrating sellar lesion causing compression and displacement of the optic chiasm and pituitary stalk with partial encasement of bilateral internal carotid arteries laterally however with intact flow voids. (C) Intensely enhancing sellar lesion can be seen on T1-weighted MRI coronal view with contrast.

≥5 mm is recommended

For tumours equal to or greater than 5 mm in size, it is important to do follow-up imaging. In the absence of any progression in 2 years, surveillance can be discontinued. For tumours showing growth surgery can be considered.^{12,13}

Surgery

Recommendation 3.3. Surgical resection is a standard treatment for symptomatic NFPAs

The standard treatment for symptomatic NFPAs patients is surgical resection (level II). The literature does not support surgical intervention as a formal recommendation in asymptomatic patients.^{6,12,15,16} Following surgical resection of symptomatic NFPAs, there is an immediate tumour volume reduction in virtually all patients, with a reported residual tumour rate of 10-36% (class III evidence). Whereas, 75-91% of patients have improved vision outcomes and 35-50% have improvement of hypopituitarism.⁶ (Figs. 01 and 03)

Indications for surgical resection are as follows:¹⁵

3.3.1. Visual deficit serves as an indication for surgery.¹⁷

The duration and severity of deficits determines the functional outcomes. Improvement is reported in about 80-90% of the cases, postoperatively at up to one-year follow-up.¹³ For macro-adenomas without visual deficit, an individualized decision is made based on disease progression.

3.3.2. Hypopituitarism is a relative indication for surgery. Recovery following surgery is varied (around 30%). After the surgery, there is a 5-10% risk of symptoms aggravation and a <5% risk of onset of Diabetes Insipidus.¹²

3.3.3. Mass effect: Pituitary adenoma rarely presents with persistent headache as a sole symptom. Therefore, it is important to rule out all other causes (preferably a neurologic consultation) before attributing it to the adenoma. Disabling headache due to mass-effect caused by lesion may be treated as an indication for non-emergent surgery, but the patient should be counselled that causality is unproven and alleviation of symptoms cannot be guaranteed. Headaches may be accompanied by nausea/vomiting.¹²

Recommendation 3.4. A thorough hormonal assessment and for preoperative clearance by an endocrinologist is warranted for all patients.

Systematic measurement of PRL is recommended, preoperatively. For macro-adenomas, it should be done with 1/100 serum dilution to counteract the hook-effect (underestimation of a very high level of PRL which is indicative of prolactinomas, otherwise). Sub-unit α level may be tested. Chromogranin A levels do not have diagnostic or prognostic value.¹³

As high as 50% of men and 25% of women presenting with NFPAs were found to have high levels of gonadotropins. It is recommended to measure systematic

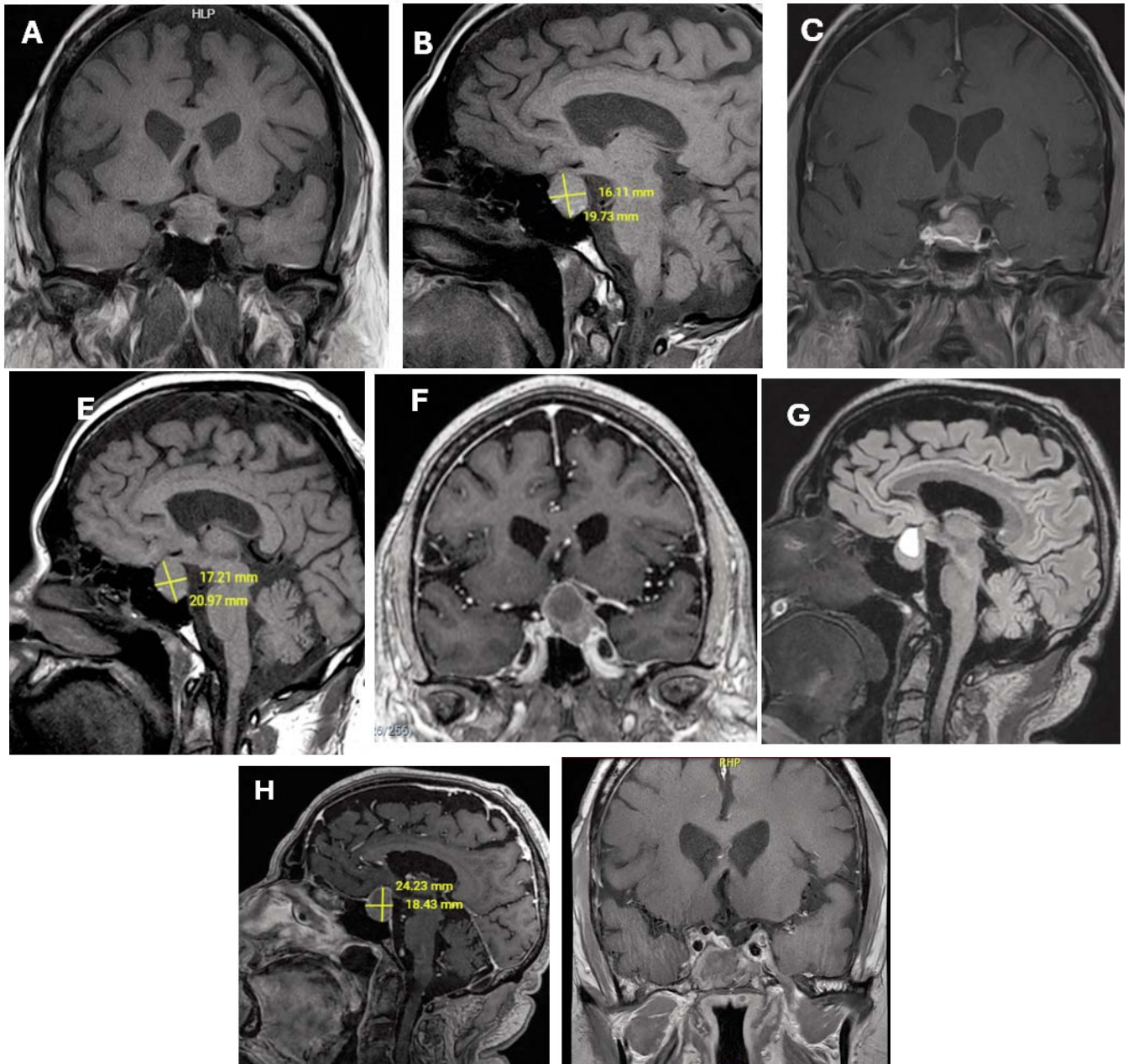


Figure-4: Macroadenoma patient with multiple comorbid. 65-year-old male, K/C of DM-II, HTN, IHD (3V CAD), unstable angina, American Society of Anesthesiologists (ASA) class IV, presented with complains of progressive vision impairment and vomiting for 8-9 months. On workup, patient was diagnosed with NFPA. Initially, follow-up with serial imaging for two years was done, as the patient was high-risk for surgery. Tumour continued to grow along-with the symptom's progression. Decision for surgical resection was made. Patient recovered well and post-operative imaging showed stable small residue, measuring 6 mm.

Pituitary protocol MRI: (A) T1-weighted coronal view showing sellar lesion with para-sellar extension, mild optic chiasm compression, and minimal bulge into sphenoid sinus. Mass is encasing the left internal carotid artery, however, flow voids are intact. (B) T1-weighted sagittal view, redemonstration of sellar lesion, measuring 19.7x16 mm. (C) T1-weighted post-contrast coronal view, shows contrast enhancing and normal pituitary gland deviated to right.

1st Follow-up scan (D) T1-weighted, post-contrast coronal view showing growth of the tumour. Tumour is expanding into supra-sellar region causing cord compression and indenting sphenoid sinus superior wall. Intra-lesional focal areas of necrosis are also visible. (E) T1-weighted sagittal images redemonstrate growing sellar lesion, measuring 21x17 mm.

2nd follow-up: (F) T1-weighted post-contrast imaging, coronal view showing growing lesion. Supra-sellar extension of the lesion and a cystic component at the superior aspect of the lesion can be seen. Tumour is encasing left internal carotid artery. (G) Cyst, with hyperintense signals, is redemonstrated in FLAIR sequence, sagittal view. (H) T1-weighted sequence, sagittal view, lesion measuring 24x18 mm.

Post-operative scan: (I) T1-weighted sequence demonstrating small residual, measuring 6 mm, alongwith the superior aspect of left internal carotid artery.

gonadotropin (LH, FSH), preoperatively. However, if levels are high, it does not affect the decision of resection.⁶ Asymptomatic hypersecretion should also be ruled out (level II) for Insulin-like Growth Factor-1 (IGF-1). If any deficiency is found in the evaluation, it should be replaced accordingly (especially for thyroid and adrenal) before surgery (level II).⁵

It is important to have these results reviewed by an endocrinologist and adjust the treatment accordingly. Preoperative optimization is important to improve surgical outcomes.

Recommendation 3.5. Surgical resection is recommended for adenomas discovered during pregnancy presenting with visual field deficit.

NFPAs with visual deficits discovered during pregnancy should be surgically resected.¹⁸⁻²⁰ In case of no compression of the chiasm, treatment can be delayed till delivery and the patient may opt for normal vaginal delivery. It is safe to breastfeed.^{13,18} When a female patient with macro-adenoma is planning for pregnancy, a surgical resection is recommended as tumours may grow during pregnancy and may cause mass effect.¹²

Recommendation 3.6. It is important to consider patient demographics, comorbidities, and medication history while planning for surgery.

Preoperative optimization of elderly patients facilitates hampering the surgery risk, making it similar to that of young patients. A trans-sphenoidal approach is preferred for patients where visual impairment is the indication of surgery. Two class-III studies on safety and treatment outcomes of transsphenoidal surgery in elderly patients supported NFPA resection in patients classified as American Society of Anesthesiologists (ASA) class I-III.¹⁶ Physiological elderly have increased risk associated with surgery. While making the decision, the benefits and risks of the procedure should be weighed.¹³(Fig 04)

Recommendation 3.7. All patients taking long-acting anti-clotting medications, preoperatively, should be switched to short-acting anti-clotting agents, followed by their resumption at an appropriate interval.

Anti-vitamin K has been reported to increase the risk of spontaneous cerebral haemorrhage by 7 to 10-fold. It should be discontinued 5 days before the surgery and heparin should be started at the same time, with the goal of normalizing INR (international normalized ratio). Anti-vitamin K can be resumed 7-14 days, postoperatively.

Anti-platelets pose an increased risk of postoperative haematoma, but abrupt preoperative discontinuation is

associated with morbidity and mortality. The cardiologist should be consulted, especially for patients with drug-eluting stents. Aspirin can be stopped 5 days prior whereas clopidogrel should be discontinued at least 10 days before the operation. They can be restarted 7-10 days after the surgery.^{3,13}

Recommendation 3.8. The decision between the trans-sphenoidal vs trans-cranial approach should be based on preoperative radiological parameters.

Trans-sphenoidal surgical resection via endoscope or microscope is the recommended approach for symptomatic NFPAs, micro- and macro-adenoma. (Level II).¹⁶ Maximal extent of resection can be achieved by optimal bony exposure of the sphenoid and sellar region. Following microscopic resection, an endoscope can be used to assess tumour remnants (Class III evidence).^{16, 21, 22} The decision for endoscopic vs. microscopic resection is dependent on the surgeon's expertise. Literature does not prefer one over the other. Better control of superior and lateral extension is a possible advantage with endoscope use.¹³

3.8.1. Giant pituitary adenoma

(GPA) ($\geq 4\text{cm}$) poses a challenge while planning a surgical approach. Surgical resection is mainly complicated by tumour extension into the surrounding structures. The operating surgeon might anticipate a complex surgery for cases like these.^{23,24} An additional tool in the surgeon's armamentarium is a combined transcranial and trans-sphenoidal approach for invasive tumours extending into the sellar region, temporal or frontal lobes (Level III evidence).¹⁶

AKU Giant Pituitary Adenoma (AGPA) score, specific to our population, takes preoperative radiological parameters, middle fossa, para-, supra- and retro-sellar extension, and internal carotid artery encasement into account and predicts the extent of resection (EOR). This score can facilitate the decision for surgical approach. A lower score correlates with a greater EOR. For tumours with a higher score, of ≥ 5 , a two-step approach may be considered.²⁵

Recommendation 3.9. Comprehensive histopathologic and molecular analysis is performed for NFPA tumour samples

WHO has sub-classified pituitary adenomas according to their histologic and molecular analysis. This classification aids in identifying tumours with a higher risk of progression so that they can be treated appropriately. Histologic work-up includes identification of the tumour receptor for accurate diagnosis. Once the sample is received by the pathologist, tumour receptors are identified to confirm the diagnosis. Samples are also tested for multiple tumour biomarkers, Ki67 expression,

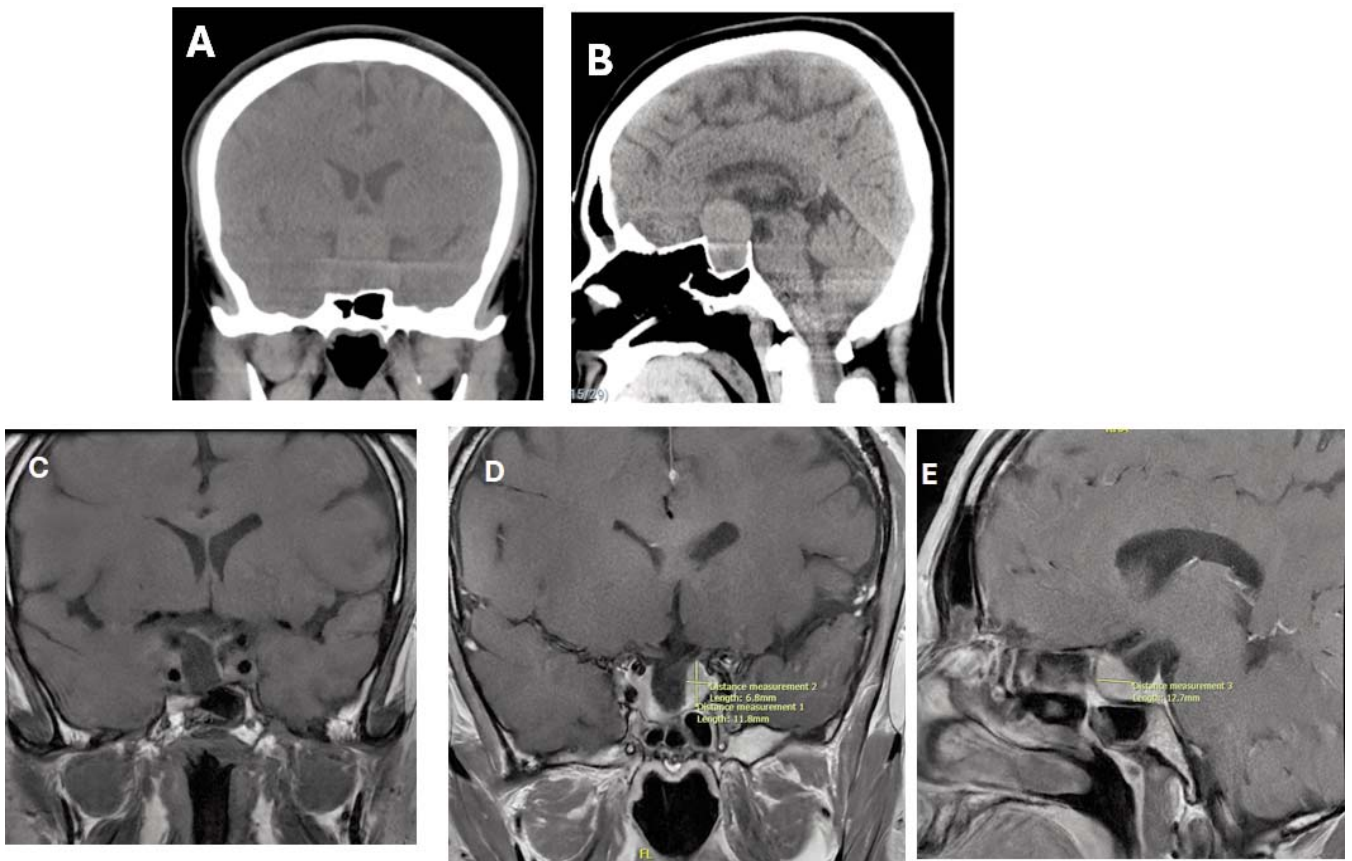


Figure-5: Radiation-induced optic neuropathy. 29-year-old male presented with decreased peripheral vision for six months. Patient was diagnosed with pituitary tumour and underwent trans-sphenoidal resection. Patient reports vision improvement following surgery, however, found to have residual along the cavernous sinus bilaterally. Patient underwent radiosurgery for the management of remnants. Post-radiation imaging shows stable bilateral residual mass. However, post-radiotherapy, patient reported worsening and blurring of vision along-with increased light sensitivity. Patient was diagnosed with radiation-induced optic neuropathy, for which steroids were prescribed.

(A) Coronal view of computed tomography (CT) showing large sellar lesion, measuring 35x25 mm. (B) CT coronal view redemonstrating sellar lesion, extending into supra-sellar region and compressing sphenoid sinus, measuring 35x24 mm.

Pituitary protocol MRI (post-radiation) (C) T1 weighted coronal MRI showing post-surgical changes, expanded sella, and residual mass along cavernous sinus, bilaterally. The mass is encasing cavernous portion of internal carotid artery bilaterally. Minimal pituitary tissue can be seen on the left and pituitary stalk is deviated towards the left side. Sagging of the optic chiasma can be seen, however it is decompressed. (D) T1 weighted coronal view showing contrast enhancing residual mass, measuring 11.8x6.8 mm, along left cavernous sinus. (E) Redemonstration of contrast enhancing mass, measuring 12.7 mm in the antero-posterior dimension. Pituitary stalk can also be visualized.

p-53 expression, and mitosis index. With advancements in technology, this knowledge continues to evolve.⁵

Literature shows that Ki67 expression signifies a risk of tumour progression and recurrence. A study reported that tumour of a high proliferative index, i.e. a Ki67 of greater than 3%, positive p53, and greater than two mitosis/10 high power fields, has a higher risk of progression and recurrence.^{15,26} Abnormal expression of any of these markers translates into the aggressive nature of the tumour. In these cases, chemotherapy is reported to be efficacious.⁵

Recommendation 3.10. Serum sodium levels and urine output monitoring in the immediate

postoperative period is crucial

Following the surgery, serum sodium levels should be checked daily while the patient is in the hospital, especially for the first two days. Similarly, hourly-to-two-hourly monitoring of urine output should be done on postoperative day 1 and 2, followed by daily monitoring.⁵ (Fig. 01)

Radiation Therapy

Recommendation 3.11 There are limited indications for the use of Radiotherapy (RT) as a first-line treatment

Radiotherapy (RT) is not recommended as a first-line treatment modality in most cases, owing to the high risk

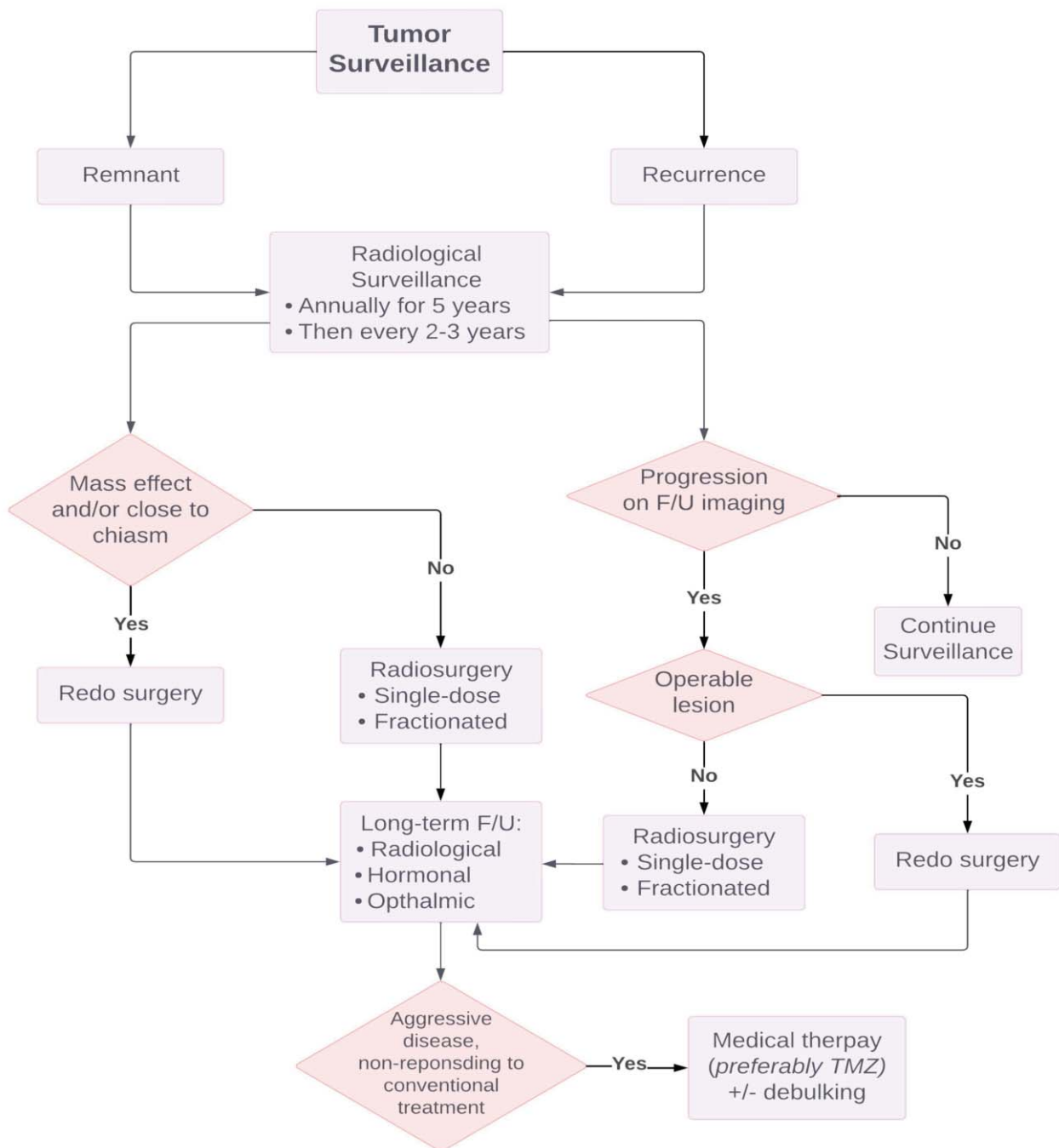


Figure-6: Algorithm outlining recommendations for the surveillance of Non-Functioning Pituitary adenoma. (Abbreviations: F/U: Follow-up; TMZ: Temozolomide)

of hypopituitarism (an overall incidence of 0-39%). Few indications for RT as first-line are tumours with a high potential of growth and patients already presenting with hypopituitarism.^{5,15,27,28}

Recommendation 3.12. Sizeable residual tumours, following surgery, should be treated with the radiotherapy

Treatment of sizeable residual tumours with RT has been widely recommended and has proven to show good tumour control. (Level II).^{5,28} Depending on the residual tumour size, tumour margin, proximity to neural structures, availability of technology, and patient's compliance with follow-up, various modalities for RT can be used.¹³ Concurrently, it is important to weigh benefits

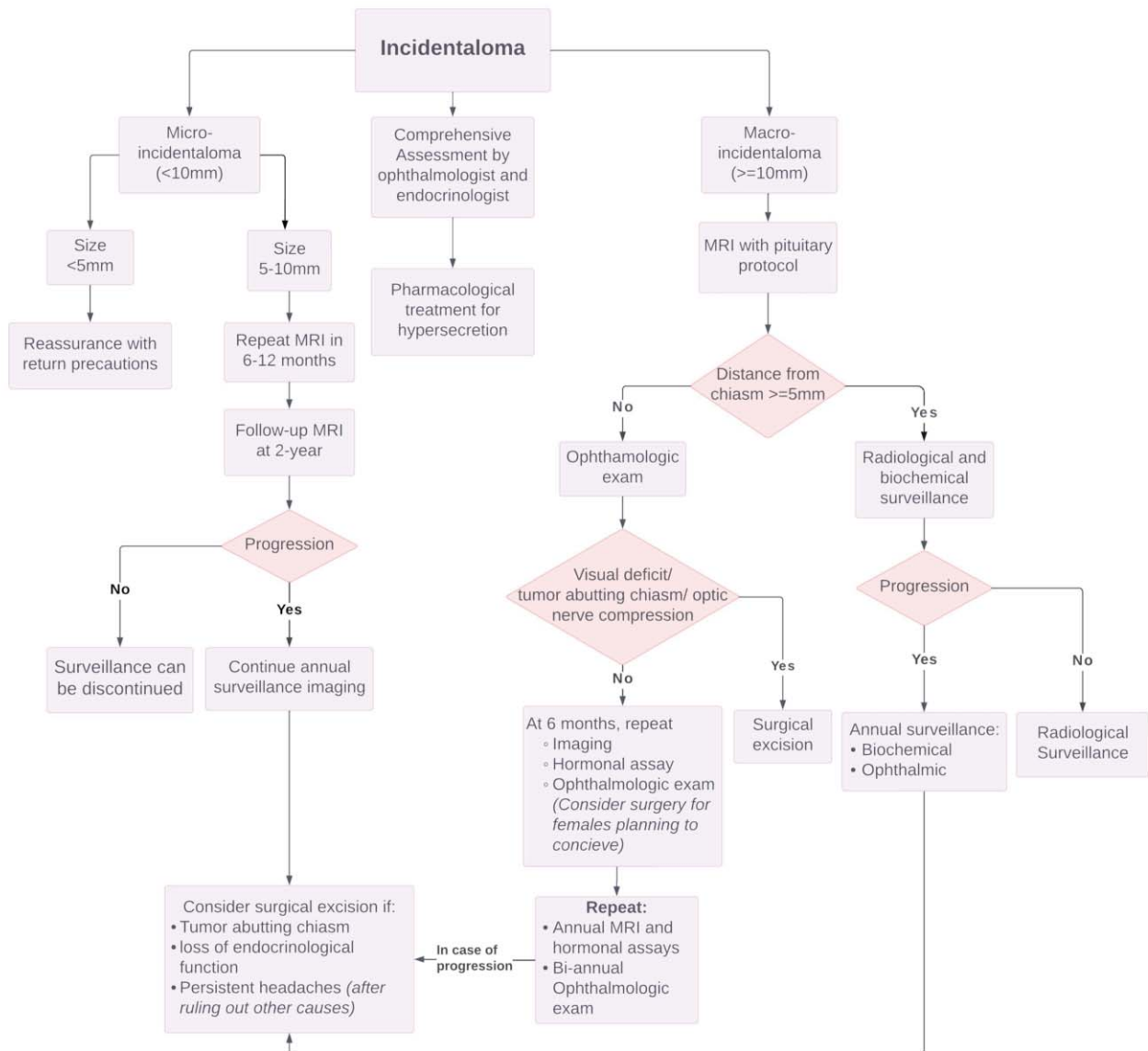


Figure-7: Algorithm describing the management of Incidentaloma
(Abbreviations: MRI: Magnetic Resonance Imaging)

against risks, mainly RT-induced hypopituitarism. Secondary tumours, radiation optic neuropathy, and vascular complications are rare complications and risk can be mitigated with stereotactic radiosurgery (SRS).^{5,13,29} (Fig. 05 and 06)

Recommendation 3.13. A radiation dose of 12 Gy for single-dose radiotherapy and 45-54 Gy for fractionated Stereotactic Radiosurgery (SRS) is recommended

A tumour control rate of 90% at a 5-year follow-up can be attained with radiotherapy: a hypo-fractionated dose of 12 Gy or fractionated dose of 45-54 Gy (25 sessions of 1.8-2 Gy). (Level III)^{13,30}

Recommendation 3.14. There should be a safe distance of 2 mm, at least, from the optic chiasm while considering RT for residual tumour measuring ≤ 3 cm Single-dose radiosurgery is the modality of choice for small (largest diameter of ≤ 3 cm)²⁹, well-defined tumours that are at a safe distance (≥ 2 mm) from the optic apparatus. This ensures no more than 8 Gy of radiation dose to the chiasm. An invasive stereotactic frame is used for precise positioning and planning (within 1mm). The desired target is superimposed and reference isodose is chosen on a high-resolution planning system. This allows a rapid decrease of the dose beyond the target, minimizing irradiation to the surrounding structures. The

range for marginal dose is 13-16 Gy.¹²

Fractionated stereotactic radiosurgery allows precise entry of multiple beams. This fractionation allows the protection of healthy tissue from irradiation, which makes it a preferable modality for tumours close to the chiasm.¹² A total dose of 45-50 Gy is divided into multiple sessions, each session has a dose of 1.8-2 Gy.¹³

Medical Therapy

Recommendation 3.15. Medical therapy for recurrent aggressive NFPAs, not responding to other interventions, should be considered. The decision is at the oncologist's discretion

Use of Temozolomide (TMZ), an oral alkylating agent, has shown promising results when used for recurrent aggressive tumours that are not responding to other interventions. Several studies have reported improved survival with the use of TMZ.^{5,12} It is critical to assess treatment response after the first three cycles and treatment should be continued for 6 more months in case of a positive response. Recurrent tumours have lower expression of O6 -methylguanine DNA methyltransferase (MGMT). Consequently, a low burden of MGMT is associated with better disease control with TMZ.^{4,13} However, MGMT is not done routinely in our country and the decision for chemotherapy use is at the oncologist's discretion.

Several studies have implied that NFPAs staining positively for dopamine or somatostatin receptors might respond to dopamine/somatostatin analogues. However, current data is not sufficient to make a strong recommendation. The decision regarding their use can be made on an individualized basis.^{4,5,12,13} (Fig. 06)

Incidentalomas

Recommendation 4.1. A comprehensive history, physical examination, biochemical evaluation, and visual assessment are required for all patients presenting with an incidentaloma

Patients presenting with the incidental finding of a pituitary tumour on imaging should undergo a detailed history, physical examination, and biochemical evaluation.³¹ All micro-incidentaloma patients mandate a limited biochemical assessment, including PRL, IGF-1 measurement, and overnight dexamethasone-suppression test if Cushing's disease is suspected. Cortisol hypersecretion screening is considered for cases of clinical Cushing's syndrome. If evidence of hyper- or hypo-secretion of the hormones is found, a more directed evaluation is mandated.

For lesions abutting optic chiasm or nerve, a formal Visual Field (VF) examination is needed. For patients where the initial diagnosis was made on a CT scan, they need to have a pituitary protocol MRI scan, if possible, for a better evaluation of the nature and extension of the pituitary incidentaloma.³² (Fig. 07)

Micro-Incidentalomas

Recommendation 4.2. Management of a micro-incidentaloma is similar to that of an asymptomatic microadenoma (recommendation 3.2)

Incidentalomas less than 5 mm do not warrant a radiologic or hormonal follow-up. Lesions with the largest diameter ≥ 5 mm require a baseline MRI at 6-12 months of diagnosis followed by appropriate surveillance.^{13,31,32} Management of these lesions is similar to that of an asymptomatic micro-adenoma (recommendation 3.2). (Fig. 07)

Macro-incidentalomas

Recommendation 4.3. Pituitary protocol MRI should be done for all macro-incidentaloma discovered on a different imaging modality

For macro-incidentalomas, the baseline workup is similar to that of a symptomatic non-functioning macro-adenoma. A pituitary protocol MRI should be performed if the incidentaloma is discovered on a different imaging modality (eg: CT scan).^{13,32} (Fig. 07)

Macro-incidentaloma management

Recommendation 4.4. For macro-incidentaloma at >5 mm distance from chiasm MRI and biochemical evaluation should be done at the one-year follow-up

For macro-incidentaloma at >5 mm distance from chiasm, it is recommended to perform an MRI after 6 months of diagnosis along with hormonal evaluation for hypopituitarism, followed by an annual surveillance for 3 years. If no progression is found, surveillance intervals can be increased. In the case of progression, hormonal evaluation is done yearly. If a lesion grows and abuts the chiasm then visual assessment should be performed. Depending on the rate of the adenoma growth and extension, surgery can be considered.^{13,32} (Fig. 07)

Recommendation 4.5. Surgery should be considered for the macro-incidentaloma close to the optic chiasm (<5 mm distance).

Surgery can be considered for macro-incidentaloma close to the chiasm (<5 mm). It is important to take the natural history of NFPAs, low risk of surgical morbidity, risk of apoplexy, surveillance compliance, and patient's plans to conceive into consideration.

When conservative management is opted for, a baseline MRI accompanied by biochemical and visual assessment should be done at a 6-month follow-up. Subsequently, VF is recommended to be repeated every 6 months along with an annual imaging and biochemical assessment. In case of progression or biochemical abnormality, treatment remains the same as that of a symptomatic NFPA.^{13,32} (Fig. 07)

Recommendation 4.6. Surgical resection is indicated when the tumor compresses the optic apparatus, results in pituitary apoplexy, or causes hypersecretion (except prolactinomas).

Surgical resection of pituitary incidentaloma is recommended for patients presenting with any of the following³³: (Fig. 07)

- Patients presenting with visual field deficits, ophthalmoplegia, or other neurological deficits
- MRI redemonstrating lesion abutting/compressing chiasm or nerve
- Pituitary apoplexy with or without visual abnormalities
- Tumours with hypersecretion (except prolactinomas)³²

Surgery should be considered in the following scenarios:

- Significant growth of lesion with new symptoms development
- Hypopituitarism/hyposecretion of hormones
- MRI redemonstrating a lesion close to the optic chiasm in a female patient planning to conceive.^{18,20}
- Persistent headache (all other causes of headaches should be ruled out first).¹²

Surveillance and response evaluation

Recommendation 5.1. Postoperative biochemical assessment is recommended every 3 months for one year followed by an indefinite 6-to-12-month follow-up, especially in instances of preoperative deficiency.

It is recommended to assess global hormonal function every 3 months for one year, postoperatively (Level III). If any deficiency is found an indefinite 6-to-12-month monitoring is warranted to tailor the replacement therapy. (Level III) If no deficiency is found the monitoring can be discontinued unless there is remnant progression/recurrence.⁵ Moreover, if adjuvant

radiotherapy is done, a 6-12 monthly monitoring is preferred. (Fig.06)

Adrenal function should be assessed in the immediate postoperative period (within two days), at 4–6 weeks, and at 12 weeks. If hypocortisolaemia is found, systematic hydrocortisone replacement is recommended. (level III) If the deficiency continues, the test should be repeated within 3 months, at least, to screen for late recovery.⁵ If the patient had a preoperative thyrotrophin deficiency, the test should be repeated postoperatively after discontinuation of thyroxine therapy for a month, at least. The literature does not report any progression of remnant/recurrence with the replacement.¹³

These recommendations are enlisted to guide management; however, each patient requires a surveillance paradigm tailored according to their case. The decision for frequency and interval of monitoring is to be made by the endocrinologist.

Recommendation 5.2. Close imaging follow-up for all NFPA cases is recommended: first scan at 3-to-6-month follow-up, second at 1 year, then annually for 5 years, followed by at 7-, 10-, and 15-year intervals.

It is important to have imaging follow-up due to a high probability of absence of neurological symptoms in case of progression. T1 and T2 MRI with fat suppression (pituitary CT only in case of MRI contraindications) are recommended (level III).⁵ Volume measured on three-dimensional (3-D) reconstructions is ideal for assessing tumour progression. However, it is not widely available, therefore, we recommend getting imaging done at the same centre every time so that variation due to the technology in use can be minimized. Pituitary MRI protocol should be followed for follow-up imaging as well. (Fig.06)

An immediate postoperative MRI is not recommended unless there is a suspected complication or when early reoperation is mandated. First MRI after surgery is usually recommended at 3-to-6-month (not before 3 months) follow-up (Level III). Acquiring imaging 6 months postoperatively reduces the probability of misinterpretation due to postoperative remodelling. Next MRI is recommended one year after the surgery. These first two images will serve as a reference for all subsequent radiological studies. NFPA's are slow-growing tumours therefore; while assessing progression, it is critical to review all available imaging, not just the preceding one. This aids in having a better understanding of the rate of progression so that gradual progression is not missed.^{5,13}

No definite length of surveillance has been identified in the literature (level III).⁵ It varies from case to case. In the absence of any adenomatous remnant, continue to obtain MRI annually for 5 years and then 7, 10, and 15 years postoperatively. Then, imaging can be repeated every 5 years.¹² Whereas, in the instance of the presence of adenomatous residue, it is recommended to obtain an MRI annually for 5 years and then repeat every 2-3 years, if the size remains stable. Follow-up can be modified according to the tumour size, distance from the optic pathways, or remnant progression. Recurrence incidence is higher 1-5 years after the surgery but may occur after 10 years. Therefore, it is important to have a close follow-up.^{12,13}

Recommendation 5.3. All NFPA patients should have close ophthalmologic follow-up/(s). In case of deficit, assessment should be done at the 3-month follow-up and then repeated every 6 months.

The literature does not recommend any specific length or frequency for ophthalmologic follow-up (level III). If no impairment is found in the first postoperative visit, then follow-up can be discontinued unless there is a remnant close to optic pathways.

In the presence of preoperative ophthalmologic deficits, a check-up consisting of VA, VF, fundus, and ocular exams should be done at 3 months post-procedure and then repeated every 6 months till the maximum improvement is reported. This is very important in a setting where the deficit is severe, and driving is contraindicated. Radiation-induced complications can occur several years after the procedure. Therefore, it is recommended to have a long-term ophthalmologic follow-up after radiosurgery. (Fig.06) Ultimately, the frequency, length, and discontinuation of surveillance are at the ophthalmologist's discretion.^{5,13}

Recommendation 5.4. Teleconsultation is a preferred mode of follow-up when the probability of patients' loss-to-follow-up is high.

Pakistan brain tumour epidemiological study reported a staggering proportion, as high as 41.45%, of the patients who were lost to follow-up. This rate increased to 43% for pituitary adenoma.^{34,35} This critical problem poses a great challenge to optimal healthcare provision in a resource-limited setting like Pakistan. Several studies, including prospective ones, from LMICs have identified the use of audio and video calls for teleconsultation as a beneficial tool for patient follow-up. Patients reported satisfaction with the quality of care provided. With the use of technology, a significant reduction in money spent, distance travelled, and missed work days was identified.³⁶⁻³⁹

In light of these findings, we recommend that in the settings where patients report difficulty in regular in-person follow-ups owing to financial, geographical, or logistic constraints, teleconsultation as a mode of follow-up should be opted. Depending on the resource availability, a healthcare setup may consider offering it to all patients for follow-up visits.

Recommendation 5.5. Post-treatment, patient counselling should be done in detail including explanations of warning signs for disease progression/recurrence.

Due to the risk of recurrence, remnant progression, hypopituitarism, and other complications following treatment, it is very important to have close follow-ups. Patients should be counselled about the risks in detail with strict return precautions. Patients should be explained that in case of worsening of symptoms, development of new symptoms, or any other relevant findings immediate medical help should be sought.

Recommendation 5.6. Surveillance for small intrasellar residual tumours is recommended. Annual serial imaging for 5 years followed by every 2-3 years.

A small intrasellar residual tumour after surgery can be followed up with serial neuroimaging, annually for 5 years then every 2-3 years. It does not mandate any intervention (Level II).⁵ Surveillance duration varies for each case and the decision lies with the medical experts.

Recommendation 5.7. Adjuvant radiotherapy ensures good disease control.

Adjuvant radiosurgery is an effective tool in the management of tumour remnants. However, studies have not shown any significant difference in outcomes of delayed (6-month postoperative) vs immediate radiotherapy.^{5,40,41} A delayed paradigm can be favored in an attempt to avoid the risks associated with RT, mainly hypopituitarism and secondary tumours. For residual tumour exhibiting progression, RT has shown a control of 90% at 10 years.¹²

Silent corticotroph adenomas (ACTH-staining tumours) with high proliferative index are recommended to be managed with an adjuvant RT (Level III).^{5,13} Tumours with gross total resection (GTR) have a low recurrence rate, and adjuvant RT is not indicated.^{13,30}

Recommendation 5.8. A multidisciplinary decision should be made when considering surgical resection of symptomatic residual tumours.

A second surgery can be considered for patients with symptomatic NFPA remnant (Level III). While making a multi-disciplinary decision regarding surgery following

factors should be taken into account:¹³

- Tumour morphology: size, relation to the optic chiasm and nerves, cavernous sinus invasion, and temporal lobe extension
- Histopathology: immunohistochemistry staining, Ki67, p53, mitosis index
- Rate of remnant growth
- Patient's demographics and compliance with surveillance
- Risk of hypopituitarism
- Accessibility and expertise of the various adjuvant treatments in the healthcare facility.

Recommendation 5.9. Both, a repeat surgical resection or RT, for the management of recurrent tumours may be considered.

In the instance of NFPA recurrence, surgical resection may be preferred for the cases where a) the entire tumour can be resected easily (no cavernous sinus invasion); b) there is a vision deficit due to optic apparatus compression, c) a safe margin of 3-5 mm is required for adjuvant RT; or d) tumour continues to progress following RT.¹ These cases are complicated, and a two-step approach can be planned to minimize the morbidity associated with surgery. Surgery might be hindered by poor intrasellar tissue differentiation and remodelling of classical landmarks (like sphenoidal rostrum and sphenoidal sinus septum). In such cases, neuro-navigation is helpful.¹³

Radiation therapy may be considered for the management of recurrence.¹⁷ It may be preferred for symptomatic recurrent tumours where the risk of surgery is high deeming the tumour inoperable (Level III). Patients require an indefinite biochemical follow-up due to the high risk of delayed hypopituitarism.^{5, 30}

Discussion

In this paper, we presented the guidelines for NFPA diagnosis, treatment, and response evaluation. NFPA is the most common macroadenoma.¹ The diagnosis and management can be complex, necessitating a multi-disciplinary approach. Existing literature was analysed in detail while synthesizing the guidelines. Certain aspects were modified considering the challenges faced in low-middle-income countries, like Pakistan. Additionally, it is critical to consider the characteristics of population demographics. In the Pakistani population, the rate of consanguineous marriage is high,⁹ and familial syndromes should be considered during clinical assessment.

Financial toxicity has been identified as a major factor affecting oncological management in LMICs.⁴² For symptomatic tumour remnant/recurrence re-resection is a preferred option, however, in a resource-limited setting financial constraints might hinder the affordability of this option. Therefore, we proposed RT/SRS as an equivocal option for such cases. Similarly, sophisticated molecular markers testing is not available at all places. Therefore, it is not included as a part of primary management in the algorithm. In cases where it is available and affordability is not an issue, its findings can be considered while devising a treatment plan. The aforementioned modifications aimed to improve the adaptation and practicality of the treatment paradigm.

Conclusion

Guidelines for accurate diagnosis, treatment, and follow-up of NFPAs are presented. Each recommendation is supported by existing literature. Concurrently, they are modified according to the demands of a resource-limited setting so that they can be adapted efficiently in LMICs. These guidelines outline the standard of care for cases of non-functioning pituitary adenomas; however, each case is unique and mandates tailored management.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Acromegaly

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Introduction

Acromegaly is a chronic disorder caused by a growth hormone-secreting pituitary adenoma, leading to raised insulin-like growth factor (IGF-1) levels.¹ Raised IGF-1 levels result in a progressive disease characterized by somatic overgrowth, leading to disfigurement and multiple comorbidities, which in turn cause early mortality or morbidity.²

The age of presentation is mid-40s, and both sexes are equally affected.³ The prevalence of acromegaly in Pakistan is 17.6% for pituitary macroadenoma and 14% for microadenoma.⁴ (Table 1). The main clinical feature is acral enlargement.⁵

Table-1: Signs and Symptoms.⁵

Enlarged acral skeleton	86%
Facial changes	• 74%
Increased perspiration	• 48%
Joint pains	• 46%
Headaches	• 40%
Hypogonadal symptoms.	• 38%
Visual defects	• 26%
Tiredness	• 26%
Weight gain.	• 18%
Galactorrhoea	• 9%

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Summary of recommendations

1. All patients with typical clinical features of acromegaly and pituitary mass should have measurements of IGF-1 levels. Serum IGF-1 levels matched for sex and age are excellent for screening, diagnosis, and monitoring.
2. In patients with normal serum IGF-1 levels, autonomous GH production should be confirmed with a 75 gm OGTT-Growth hormone suppression test.
3. A pituitary MRI is indicated following clinical and biochemical confirmation of Acromegaly.
4. Visual field testing (Perimetry) and pituitary hormonal testing are recommended.
5. Acromegaly-related comorbidities, such as hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnoea, should be evaluated.
6. The treatment goal is to control elevated GH and/or IGF-I levels, improve signs and symptoms of the disease, and reduce mortality rates.
7. Therapeutic targets are age-normalised serum IGF-1 levels and growth hormone of less than 1ng/ml for first-generation assays and 0.4ng/ml for third-generation assays (which are still unavailable in Pakistan) after doing OGTT
8. First-line therapy is surgical resection of pituitary tumours.
9. Ideally, medical therapy is the second-line therapy recommended worldwide. However, due to cost constraints and unavailability, we recommend Adjuvant therapy, i.e., radiosurgery/radiation therapy, as second-line therapy for patients with persistent disease despite surgery. If medical therapy is available and affordable, then guidelines remain the same

as international.

10. Given resource constraints in lower and middle-income settings, we recommend medical therapy as a third-line treatment for acromegaly. However, it may be used as a second-line treatment when available and affordable.
11. Medical therapy is also indicated as bridging therapy in patients with persistent diseases after radiotherapy till the effects of radiotherapy are visible.
12. Re-surgery is recommended or a combination of available medical therapies if the patient is still biochemically not cured.
13. Treatment of Acromegaly comorbidities is recommended to reduce morbidity and mortality.

Recommendations

Diagnosis

• Recommendation 1: serum IGF -1

Age and sex-matched serum IGF1 levels should be tested in all patients with acromegalic acral and facial features. All patients who have presented with pituitary adenoma must have IGF-1 to rule out acromegaly.

Random Growth Hormone: A Random growth hormone test is not diagnostic for acromegaly; hence, it should not be performed.³

• Recommendation 2: 75gm Oral Glucose Tolerance Test (OGTT) growth hormone suppression test

Confirmation of the diagnosis is recommended with a 75 gm OGTT, especially in patients with equivocal IGF-1 levels that are IGF-1 <1.3 fold the upper normal limit and the patient has acromegalic features.⁶

This is the most specific dynamic test for establishing the diagnosis of acromegaly.⁷

The test protocol is to give the patient 75 gm of glucose orally and measure growth hormone and glucose levels at 0, 30, 60, 90, and 120 minutes. Acromegaly is diagnosed if GH concentration is greater than 1 ng/ml or 1 μ g/L. In normal persons, GH levels fall to <1 ng/ml within two hours of taking 75 g glucose.⁷ This test is not recommended in patients with typical symptoms and raised IGF-1 levels.⁶

• Recommendation 3: Imaging

Following clinical and biochemical confirmation of Acromegaly, a Pituitary MRI should be done to confirm

the size and extent of the pituitary lesion.²

• Recommendation 4: Perimetry and other Pituitary Hormones

Visual field testing (Perimetry) should be performed to rule out compression of the optic chiasma.³ All pituitary hormones, such as Serum Prolactin, TSH, FT4, 8 am Cortisol, FSH, LH, Testosterone level (male patient), and Estradiol level (female patient), need to be tested to rule out hypopituitarism and co-secretion, especially prolactin co-secretion.⁸

• Recommendation 5: Evaluation for Comorbidities

Every acromegaly patient must be evaluated for comorbidities, such as hypertension,

Diabetes Mellitus, cardiovascular disease, osteoarthritis, and sleep apnoea.⁶

If there are palpable thyroid nodules, then a thyroid ultrasound is indicated.⁶

A colonoscopy at diagnosis is recommended for colonic neoplasia.⁹

• Recommendations 6 & 7: Treatment goals (1)

Achieve sex and age-normalised serum IGF-1 levels. OGTT suppressed growth hormone levels of less than 1ng/ml (first-generation assay) or 0.4 ng/ml (third-generation assay).

Reduction in size of pituitary adenoma as well as in its local mass effects.

Improvement in signs and symptoms of the disease.

Improved medical comorbidities, hence mortality.

Maintenance of overall pituitary functions.

Management of Acromegaly (Figure 1)

Studies have strongly suggested that a therapeutic plan for every patient should be devised using a multidisciplinary team approach consisting of an endocrinologist, an experienced neurosurgeon, a dedicated radiation oncologist, and a radiation therapist. This approach would improve outcomes and reduce mortality.¹⁰

• Recommendation 8: Surgical Therapy (Figure 1)

First-line therapy is surgical. The preoperative factors which are predictors of surgical cure are:¹¹

- ▶ Size and Appearance of the tumour on MRI pituitary
- ▶ GH and IGF-I levels

Trans-nasal procedures have shown improved postoperative outcomes and shorter hospital stays. However, it must be performed by experienced surgeons.¹⁰ Surgical adjuncts like a) intraoperative

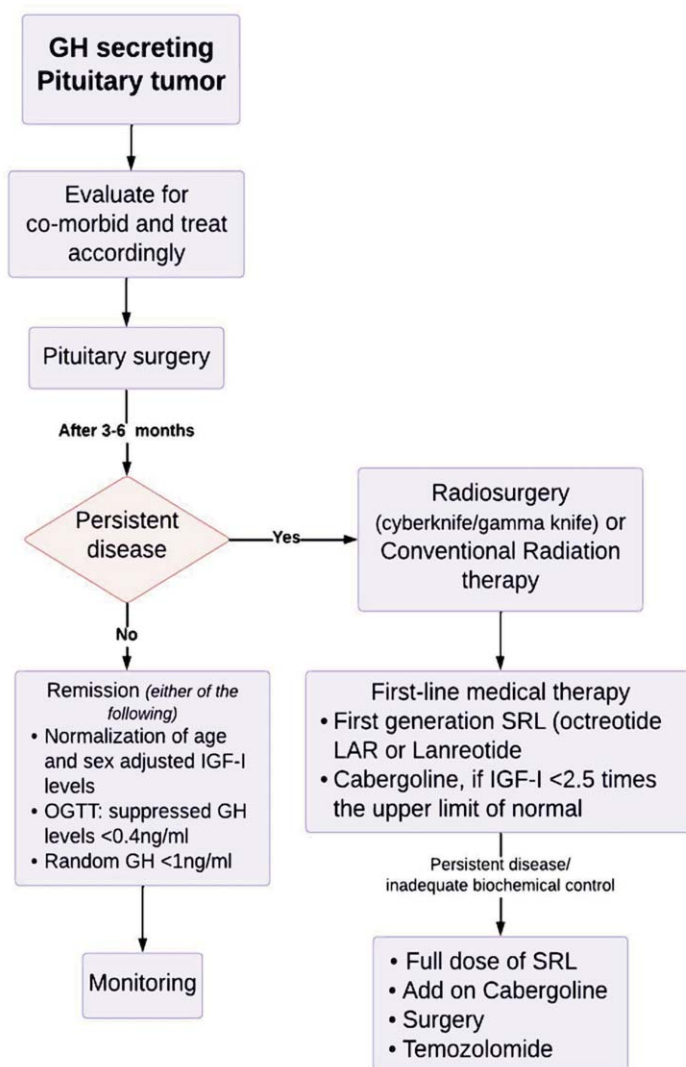


Figure-1: Algorithm describing management of acromegaly..

imaging, (b) neuro navigation, and (c) intraoperative determination of GH levels can be used to improve outcomes.¹²⁻¹⁴ However as these are not available in Pakistan we do not recommend them.

For giant pituitary adenomas (≥ 4 cm) TSS alone might not provide sufficient tumour exposure. Therefore, it is critical to assess on pre-operative imaging if the tumour extends into the middle cranial fossa, suprasellar, or retrosellar compartments. In that case two-staged approach, TSS followed by trans-cranial resection, is recommended. These cases are unique and mandate consultation with a neurosurgeon who is an expert in pituitary surgeries.¹⁵

• Preoperative Somatostatin Analogues

The administration of a preoperative somatostatin

analogue in patients with massive invasive microadenoma resulted in short-term biochemical control and cure of acromegaly; however, there were no long-term benefits.¹⁵ Hence, this practice is not recommended.

• Post-Op Assessment and Cure

During the immediate post-op period, posterior pituitary function must be checked for at least two weeks. Post-op Assessment of the pituitary axis for hypopituitarism, especially the adrenal axis, should be done.

MRI pituitary for residual tumour should be done at least 12 weeks after surgery.

Biochemical activity for acromegaly should be assessed at 3-6 months by doing IGF-1 levels. After achieving the age and sex-matched IGF1 levels, OGTT for growth hormone should be done to confirm cure, which will be defined as suppressed levels of growth hormone less than 1ng/dl (old generation assays) or 0.4ng/ml (3rd generation assays).¹⁶ As the old/first-generation assays are still in use in the country, suppressed growth hormone levels of 1ng/dl are recommended to be considered as a cure. This will continue until the new-generation assays are made available.

• Recommendation 9: Radiation Therapy (Figure 1)

Patients with persistent disease, despite surgery, those showing poor response are intolerant, or cannot afford medical therapy, are eligible for radiosurgery.¹⁷ Although international guidelines recommend medical therapy as a second step in the management of acromegaly, because of the unavailability and price factor of the medicines, stereotactic surgery is recommended in such patients. However, if medical therapy is accessible and affordable, it remains the preferred second-line option.

• Recommendations 10 & 11: Medical Therapy (Figure 1)

Medical therapy is internationally recommended as second-line therapy for patients with persistent disease despite surgical resection of the adenoma and for patients in whom surgery is not appropriate.¹⁶ However, we keep this as the third step due to unavailability and financial constraints.

We are recommending medical therapy as interim therapy or bridging therapy post-radiation therapy till the cure is achieved.

First-line medical therapy

1. Somatostatin Receptor Ligands

Somatostatin receptor ligands are somatostatin analogues that are growth hormone inhibitors.¹⁸ These first-generation somatostatin analogues Octreotide and Lanreotide, have reported a 55% biochemical response and a greater number of patients with improved symptoms. SRL also leads to a reduction in adenoma size by 20-40%.¹⁹

► Dose

Octreotide 20 mg per month: If levels do not decrease after two months, the dose can be increased to 30mg/month and 40 mg/month.

Lanreotide 60-120mg every four weeks or high frequency, i.e., every 21 days.

► Side effect

Side effects of SRL are usually Gastrointestinal problems like diarrhoea, steatorrhea, constipation, gall stones, hair loss, bradycardia, local injection site irritation, and pain.¹⁹

Oral somatostatin ligands

Two oral preparations have been developed: Oral Octreotide Capsules (OOC) and Paltusotine, which have shown equivalent results as injectables. However, more work needs to be done on their effect on tumour size. As they are not available in Pakistan; hence, no final consensus has been made on them.²⁰

2. Dopamine Agonist (Cabergoline)

Biochemical control by Cabergoline as monotherapy can be achieved in one-third of the patients.²¹

► Indication

If IGF-1 is high but not more than double and a half (2.5) of the upper normal limit, then dopamine agonists should be given either as monotherapy or in combination with the Sandostatin analogue.²²

► Dose

The dose can be started at 0.5mg once weekly or 0.25mg twice weekly and built up to 1 gm twice weekly.

► Side effects

Common side effects include GI disturbances, postural hypotension, headache and nasal congestion.

Second-line medical therapy

1. In partial response, i.e., a decrease in GH and IGF >50% after taking SRL as first-line therapy, the SRL's dose and frequency can be increased.²³
2. Dopamine agonists can be added to the SRL therapy if IGF1 Levels remain modestly high.²²

3. Individualized treatment is recommended if the patient is not responding to the maximum dosage of first-line SRL. The factors affecting the choice of second-line medication will be as follows:

- Presence of residual tumour,
- Impaired glucose tolerance.

Internationally, it is recommended that in case of a residual tumour, the patient should be started on Pasireotide LAR, and if there is severe hyperglycaemia, Pegvisomant is the choice.^{23,24} However, as it is unavailable in Pakistan, we recommend moving toward re-surgery wherever possible.

a. Pasireotide (not available in Pakistan)

Pasireotide Lar is a somatostatin analogue. The dose given is 4mg/month. The main side effect is hyperglycaemia, which requires insulin therapy. Pasireotide has shown remarkable results. After six months of therapy, 66% of patients gained control of acromegaly.²⁵

b. Pegvisomant (not available in Pakistan)

Monotherapy as second-line therapy with Pegvisomant, a growth hormone receptor antagonist, leads to 90% biochemical control in clinical trials; however, in clinical practice, only 60% control has been observed. This difference is attributed to not prescribing maximum doses in clinical practice.²⁶

► Dose

The starting dose is 10mg/day and can be increased by following IGF-1 levels. The maximum dose is 30mg/day

► Side effects

The main side effect observed is the disorder of liver function. Monthly monitoring of liver function is recommended. There is also the risk of an increase in the size of the pituitary tumour.

Other side effects are lipodystrophy at the injection site as well as at distant sites.

• Recommendation 12: Further Treatment If Still Biochemically Uncontrolled (Figure 1)

1. Surgical Intervention (Or Re-intervention): This is the recommended treatment procedure in Pakistan.
2. Combination Therapy: This depends on the availability of medical therapy. Studies have shown better results for combination therapy than monotherapy.¹⁹

Table-2: Criteria for response to somatostatin analogues 12 months of treatment according to Colao, et al.²⁸

Type of response	Definitions
Full response	Normalisation of growth hormone and IGF-1 levels and 20% reduction in size of the tumour in patients 1. Treated with first-line medical therapy. OR 2. Second line medical therapy medical therapy OR 3. Those with no tumour on MRI at baseline
Partial response	1. A >50% decrease in GH and/or IGF-I levels without control 2. And/or >20% reduction in size of tumour when treated with first- or second-line medical therapy.
Poor response or resistance	1. A nonsignificant fall in GH and IGF-I levels without control 2. No reduction in tumours of patients treated on the first line. 3. Increase in tumour size in any patient.

3. **Temozolomide:** Temozolomide is methylating chemotherapy. It can cross the blood-brain; hence, it is frequently used to treat brain tumours. In the case of acromegaly, it is used in close collaboration with the neuro-oncologist, especially in aggressive or malignant pituitary tumours. The published response rate of this treatment is 48% to 65%, and progression-free survival (PFS) is 34 months, but due to insufficient data and studies, the overall survival (OS) is still not known.²⁷ (Table 2)

• Recommendation 13: Treatment Of Comorbidities

1. Thyroid nodules

A neck examination of the thyroid and an ultrasound of the neck should be done at the time of diagnosis and repeated annually. Any changes found should be followed and treated as generally done.²⁸

2. Sleep apnoea

Patients with clinical signs of sleep apnoea should have polysomnography at diagnosis. Follow-up should be done using the Epworth scale. If the patient has severe sleep apnoea, intensive medical therapy should be given at least six months before surgery.²⁹

3. Diabetes/dyslipidaemia

Diabetes treatment should be optimised. All anti-diabetic medications can be given to stabilise glycaemia.²⁵ Pasireotide is contraindicated in diabetic patients;³¹ on the other hand, Pegvisomant can be considered in patients with uncontrolled diabetes.²⁶

4. Treatment of acromegaly leading to GH deficiency

The risk-to-benefit ratio of replacing growth hormone is still not clear, and it is expensive, so it may be considered only if there are severe symptoms of growth hormone deficiency and the patient can afford it.²⁹

5. Evaluation for Vertebral Fractures

If there is clinical suspicion of vertebral fractures, a radiological evaluation of the spine should be performed. Other causes, like vitamin D deficiency, hypogonadism and hypoparathyroidism, should also be evaluated. Optimising the treatment of acromegaly is essential in case of active disease.²⁹

6. Cardiovascular Diseases

- An Electrocardiogram should be done at the time of diagnosis.
- 24 h Holter monitoring should be done if there are arrhythmias.
- An echocardiogram can be done at the time of diagnosis. If a patient having active acromegaly has hypertension and /or diabetes, then regular follow-ups along with an echocardiogram should be carried out.
- Preoperative treatment for at least 3-6 months is needed and should be continued until GH/IGF-1 reduction if there is cardiomyopathy. This treatment does not have an effect on postoperative medical therapy for acromegaly; however, it should be optimized.³⁰
- If there is clinical evidence of ischaemic heart disease, then a stress test should be done.³¹
- There is no consensus; however, a dopaminergic is contraindicated in patients with prior valve disease.

7. Polyps and colorectal carcinoma

- At the time of diagnosis of acromegaly, a colonoscopy should be performed.
- All polyps and adenomas should be removed to reduce the possibility of colorectal cancer.

- General population recommendations should be followed if colonoscopy is normal and acromegaly is controlled.
- If the colonoscopy is normal and there is uncontrolled acromegaly, a colonoscopy should be done every 3-5 years.
- Colonoscopy should be done as recommended for patients with colonic lesions if the colonoscopy findings are abnormal with controlled acromegaly.²⁹

8. Ambulatory Hypertension (AHT)

- Blood pressure measurements should be done on all patients.
- Follow-up every six months is recommended for patients with active acromegaly and doubtful blood pressure readings.
- In patients with active acromegaly and hypertension, annual follow-up is recommended.
- Follow up after every change in antihypertensive treatment
- ACEI or ARB are the treatment options recommended.^{31,32}

9. Osteoarthritis

Osteoarthritis and other osteoarticular diseases need to be evaluated and managed at the time of diagnosis and require regular follow-up.^{33,34}

Discussion

This guideline focuses on diagnosing and treating acromegaly, a condition caused by excess growth hormone, in settings with limited resources. Our challenges are limited access, shortage, and the cost of medications such as Somatostatin analogues, Pegvisomant, and Pasireotide. Hence, the recommended treatment based on availability and cost is first-line surgery, second-line stereotactic therapy, and third-line medical therapy. Mainly recommended are SRL and Cabergoline alone or in combination as medical therapy. It is also recommended, that medications should be used temporarily as a bridging therapy after radiosurgery to control hormone levels until they are stabilized. If the disease persists, surgery is the choice of treatment.

Conclusion

These guidelines prioritize readily available and affordable therapies while aiming for effective acromegaly management.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Prolactinoma

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Introduction

Prolactin (PRL) is a polypeptide hormone containing 198 amino acids and having a molecular weight of 22,000 daltons which is secreted by lactotroph cells in the adenohypophysis or anterior pituitary gland. It circulates in different molecular sizes— small form, large form, and a larger form with molecular weights of 22,000, 50,000, and >100,000 respectively. Most (80%) of PRL is secreted in a small form which is biologically active. PRL has a short half-life of 20 minutes and is one of the stress hormones.¹ It is released in a rhythmic pattern characterized by pulses, exhibiting a circadian rhythm associated with sleep. Its levels peak during the early morning and gradually decrease during the afternoon. The primary action of PRL is the stimulation of breast development along with oestrogen during pregnancy and plays a vital role in the commencement and support of lactation.¹ PRL leads to suppression of LH and FSH secretion during pregnancy and thus inhibits ovulation. Prolactinomas; which are tumours that secrete PRL, remain the most frequent type of pituitary adenomas, representing nearly half of all pituitary tumours that require medical consideration.²⁻⁵

Clinical features of hyperprolactinaemia⁵⁻⁹

Females:

- Galactorrhoea
- Oligo-amenorrhoea

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- Subfertility
- Osteopenia/osteoporosis

Males:

- Gynaecomastia
- Galactorrhoea (rarely)
- Reduced libido.
- Erectile dysfunction
- Subfertility
- Osteopenia/osteoporosis

Causes of hyperprolactinaemia^{1,2,10}

Physiological (transient or temporary hyperprolactinaemia)

- Pregnancy
- Lactation
- Exercise
- Coitus
- Nipple stimulation
- Stress
- Seizure

Macroprolactinaemia

- Immunoglobulin (IgG) binding PRL

Hypothalamic/ pituitary lesions

- **Prolactinoma**
- **Non-functioning masses by causing stalk effect**
*adenoma, craniopharyngioma, meningioma, Rathke's cleft cyst

- **Inflammatory/infiltrative lesions:** lymphocytic hypophysitis, Langerhans cell histiocytosis

- Empty sella syndrome
- Pituitary stalk section

Other illness

- **Hypothyroidism** (TRH causes elevation of PRL along with TSH) **

Chronic renal failure (high serum PRL concentration by reduced PRL clearance; this normalizes after renal transplantation)

Neurogenic:

- Breast stimulation
- Chest wall lesions
- Spinal cord lesions

Drugs

Drugs lead to PRL elevation by dopamine antagonism ***

- Antiemetics: (metoclopramide, domperidone)
- Antipsychotics: (risperidone, levosulpiride, amisulpride, paliperidone, haloperidol)
- Antidepressants (uncommon)
- Oestrogens
- Verapamil
- Opioids

Ectopic secretion of PRL

- Renal cell carcinoma
- Perivascular epithelioid cell tumours
- Gonadoblastoma
- Ovarian teratoma

**Stalk effect or stalk compression can occur due to tumours or other masses within or near the pituitary gland compressing the pituitary stalk, resulting in diminished dopamine delivery to the pituitary and, consequently, disinhibition of the lactotrophs.*

***Thyrotroph hyperplasia in the setting of primary hypothyroidism can be mistaken for pituitary adenoma, thus caution is needed to avoid mismanagement.*

****Most of the drugs cause PRL elevation below 100 ng/ml (2127 mIU/L), however, Risperidone and metoclopramide can lead to PRL elevations up to 200 ng/dl (4255 mIU/L)*

Association of clinical features with a degree of hyperprolactinaemia:⁶

Mild hyperprolactinaemia: Mild degrees of hyperprolactinaemia, eg, serum PRL values of 20 to 50 ng/mL (426 to 1064 mIU/L) may lead to only inadequate progesterone secretion resulting in a short luteal phase of the menstrual cycle. Even in the absence of menstrual cycle irregularities, mild hyperprolactinaemia can lead to subfertility, affecting approximately one-fifth of women undergoing subfertility evaluation.

Moderate hyperprolactinaemia: Moderate degrees of hyperprolactinaemia, eg, serum PRL values of 50 to 100 ng/mL (1064 to 2127 mIU/L), result in either amenorrhoea or oligomenorrhoea.

Severe hyperprolactinaemia: A serum PRL level greater than 100 ng/mL (2127 mIU/L) is characteristically

associated with overt hypogonadism, insufficient oestradiol release, and its effects, including amenorrhoea, hot flashes, and vaginal dryness.

Prolactinomas (Lactotroph adenomas):¹⁰

Prolactinomas are benign tumours of the lactotrophs. Serum PRL concentrations can vary widely in patients who have lactotroph adenomas with ranges that are only slightly elevated to 50,000 ng/mL (1063830 mIU/L); in comparison, in hyperprolactinaemia due to other causes, the levels of Prolactin seldom surpass 200 ng/mL (4255 mIU/L).

Summary of recommendations

Recommendation 1.1: The clinician should consider certain pitfalls in the diagnosis of hyperprolactinaemia

Recommendation 1.2: The clinician should take a detailed history and relevant work-up to rule out other possible causes of hyperprolactinaemia

Recommendation 1.3: Confirm hyperprolactinaemia on two separate occasions in borderline cases

Recommendation 1.4: Assess prolactin levels after drug withdrawal in symptomatic drug-induced hyperprolactinaemia

Recommendation 1.4a: Dynamic tests are not required in the assessment of hyperprolactinaemia.

Recommendation 1.5: Obtain a pituitary MRI with and without contrast after other reasons for hyperprolactinaemia have been excluded

Recommendation 1.6: Assess anterior pituitary hormonal function in patients with macroprolactinoma on Pituitary MRI

Recommendation 1.7: In patients with macroprolactinoma on Pituitary MRI where the tumour is abutting or impinging the optic chiasm; visual field assessment with formal perimetry should be obtained.

Recommendation 2.1: Offer medical treatment with Dopamine agonists (11) to patients with prolactinoma to normalize prolactin level, reduce tumour size and restore gonadal function

Recommendation 2.2: Offer medical treatment with cabergoline as a first-line treatment to patients with prolactinoma

Recommendation 2.3: Monitor for side effects of DAs

Recommendation 2.4: Initiate DAs at the lowest dose and gradually up-titrate the dose to achieve

normalisation or near-normalisation of prolactin level

Recommendation 2.5: Offer hormone replacement therapy (HRT) to women with macroprolactinomas who do not desire fertility and lack the symptoms of troublesome galactorrhoea

Recommendation 2.6: Offer hormone replacement therapy in men with micro prolactinomas who are intolerant or resistant to DAs and do not desire fertility and hCG treatment to those who desire fertility

Recommendation 3.1: Consider trans-sphenoidal surgery for prolactinoma when there is resistance or intolerance to medical treatment

Recommendation 4.1: Consider postoperative radiation therapy in patients with drug-resistant macroprolactinoma after surgical debulking

Recommendation 5.1: Consider serial monitoring of patients on DAs through prolactin level

Recommendation 5.2: Perform serial assessment of visual fields through formal perimetry if there were evident initial visual field defects

Recommendation 5.3: Obtain serial pituitary MRI in patients with macroprolactinoma for periodic monitoring.

Recommendation 5.4: Manage comorbidities in patients undergoing treatment for prolactinoma

Recommendation 6.1: Offer DAs as initial treatment to patients with macroprolactinoma and visual field defects

Recommendation 7.1: Consider withdrawal of DAs in patients who have achieved long-term normalization of prolactin level and the tumour size has reduced significantly

Recommendation 7.2: Keep patients on periodic follow-up after withdrawal of DAs as there can be a risk of recurrence

Recommendation 8.1: Get baseline and serial echocardiography in patients requiring long-term cabergoline at doses that are more than 2 mg per week

Recommendation 9.1: Manage resistant prolactinomas in tertiary care centres with the expertise and availability of a multidisciplinary team

Recommendation 10.1: Consider an individualized approach to managing women with prolactinoma anticipating pregnancy and during pregnancy.

Recommendations

Recommendation 1.1: The clinician should consider certain pitfalls in the diagnosis of hyperprolactinaemia

A) Hook effect: It is important to exercise caution when interpreting serum PRL concentrations ranging from 20 to 200 ng/mL (426 to 4255 mIU/L) in the presence of a macroadenoma, as there is a potential for artificially low values due to the phenomenon known as the "hook effect." This effect occurs when a very high serum PRL, eg, 5000 ng/mL (106383 mIU/L) interferes with the immunoassay system resulting in false low prolactin estimation due to inhibition of immune complex formation by extra antigen concentration. The result is a spurious PRL concentration that is only modestly elevated, signifying that the macroadenoma is clinically nonfunctioning. The artefact can be evaded by repeating the assay by using a 1:100 dilution of serum.^{10,11}

B) Macroprolactin: Macroprolactinaemia is a condition characterised by increased

levels of PRL due to reduced clearance, primarily caused by the presence of macroprolactin. Macroprolactin refers to aggregates of PRL and antibodies, specifically anti-prolactin autoantibodies, ranging in size from approximately 150 to 170 kD. It's worth noting that the predominant form of native PRL in the bloodstream is 23 kD in size.

Although macroprolactin aggregates are detectable through immunological assays, they do not exhibit biological activity, resulting in no discernible clinical symptoms. Nonetheless, macroprolactin holds indirect clinical significance because it can lead to misdiagnosis and inappropriate treatment as PRL hypersecretion. To avoid such misdiagnosis, it is advisable to request the laboratory for pre-treatment of serum samples with polyethylene glycol, which precipitates macro prolactin, before conducting the PRL immunoassay.^{10,11}

Recommendation 1.2: The clinician should take a detailed history and relevant work-up to rule out other possible causes of hyperprolactinaemia (Figure 1)

A detailed history, including ruling out the potential causes of hyperprolactinaemia other than prolactinoma. It is essential to rule out pregnancy, causative drugs, and history of renal disease. Enquire about headache, visual symptoms, symptoms of hypothyroidism, hypogonadal symptoms, gynecomastia in men and galactorrhoea in women. Physical examination should be directed toward the assessment of chiasmal compression (e.g., bitemporal

field loss), for chest wall injury, and signs of hypothyroidism or hypogonadism.⁶

Thyroid status and renal function should be evaluated and pregnancy should be ruled out in women of reproductive age.²

Recommendation 1.3: Confirm hyperprolactinaemia on two separate occasions in borderline cases

Confirm hyperprolactinaemia on two separate occasions in equivocal cases (borderline high PRL level).²

Hyperprolactinaemia is diagnosed when the serum PRL concentration is well above the normal reference range; >20 ng/mL [425.5 mIU/L] in men and postmenopausal women and >30 ng/mL [636 mIU/L] in premenopausal women.

Meals may stimulate PRL secretion marginally; thus, an initial serum PRL concentration is only slightly elevated (21 - 40 ng/mL [447 - 851 mIU/L]), and the test should be repeated on a fasting sample before the patient is labelled with hyperprolactinaemia. (12)

Given that circulating PRL has a half-life of 20 to 50 minutes, a pooled sample analysis (using pooled serum from three samples of PRL taken half an hour apart) can be an effective method to differentiate true hyperprolactinaemia from elevated PRL levels caused by venipuncture stress. This approach helps prevent the over-diagnosis of hyperprolactinaemia in patients who initially present with mild hyperprolactinaemia.¹³

Recommendation 1.4: Assess prolactin levels after drug withdrawal in symptomatic drug-induced hyperprolactinaemia (Figure 1)

When dealing with symptomatic patients experiencing drug-induced hyperprolactinaemia, the initial priority is to determine if it is possible to discontinue the medication and replace it with an alternative that does not induce hyperprolactinaemia. Subsequently, it is advisable to re-evaluate the prolactin (PRL) levels by conducting another PRL test after one week.¹⁰ Switching of the antipsychotic drug should not be done without consultation with the patient-physician. MRI pituitary may be obtained to differentiate between drug-induced hyperprolactinaemia and hyperprolactinaemia secondary to a pituitary lesion if the onset of hyperprolactinaemia does not coincide with medication initiation.

If the risks of discontinuing the drug outweigh the potential benefits, appropriate sex hormone replacement should be offered for long-term hypogonadism secondary to drug-induced hyperprolactinaemia.

Recommendation 1.4a: Dynamic tests are not required in the assessment of hyperprolactinaemia.

Recommendation 1.5: Obtain a pituitary MRI with and without contrast after other reasons for hyperprolactinaemia have been excluded (Figure 1)

Pituitary MRI: We recommend getting a Pituitary MRI with and without contrast after ruling out other causes, with confirmation of hyperprolactinaemia on two separate occasions in equivocal cases or significantly high PRL levels in patients with evident clinical features of hyperprolactinaemia.^{2,10}

Relationship between prolactinoma and prolactin concentration:

PRL levels characteristically correlate to the tumour size in direct proportion. PRL level below 200 ng/ml (4255 mIU/L) relates with < 1 cm of tumour size. The PRL level between 200 ng/ml (4255 mIU/L) - 1000 ng/ml (21277 mIU/L) corresponds with 1 cm to 2 cm of tumour size. The PRL level which is > 1000 ng/ml (21277 mIU/L) is proportional to > 2 cm tumour diameter. After ruling out the hook effect, if the prolactin (PRL) level does not correlate with the size of the tumour, it could be due to either a significant cystic component within the tumour or an undifferentiated prolactinoma.^{14,15}

Macrolactinoma (>1 cm tumour size) is more common in males not only due to late recognition of symptoms and diagnostic delay but, rather, to the higher proliferative potential of the tumours. Typically, these tumours exhibit greater invasiveness and show reduced responsiveness to bromocriptine (BRC) therapy. The underlying molecular mechanisms responsible for these differences remain uncertain. These observations emphasize the need for a more proactive therapeutic approach to PRL-secreting tumours in males compared to females.^{6,10}

Recommendation 1.6: Assess anterior pituitary hormonal function in patients with macrolactinoma on Pituitary MRI

Assess anterior pituitary function in patients with a macrolactinoma. FT4, Cortisol (8-9 am), IGF-1, testosterone & LH/FSH (males), Estradiol & LH/FSH (females).^{2,10}

Recommendation 1.7: In patients with macrolactinoma on Pituitary MRI where the tumour is abutting or impinging the optic chiasm; visual field assessment with formal perimetry should be obtained (Figure 1).

If the tumour is abutting or impinging on the optic chiasma, formal perimetry should be done. This will assess the baseline visual field defect which can be monitored

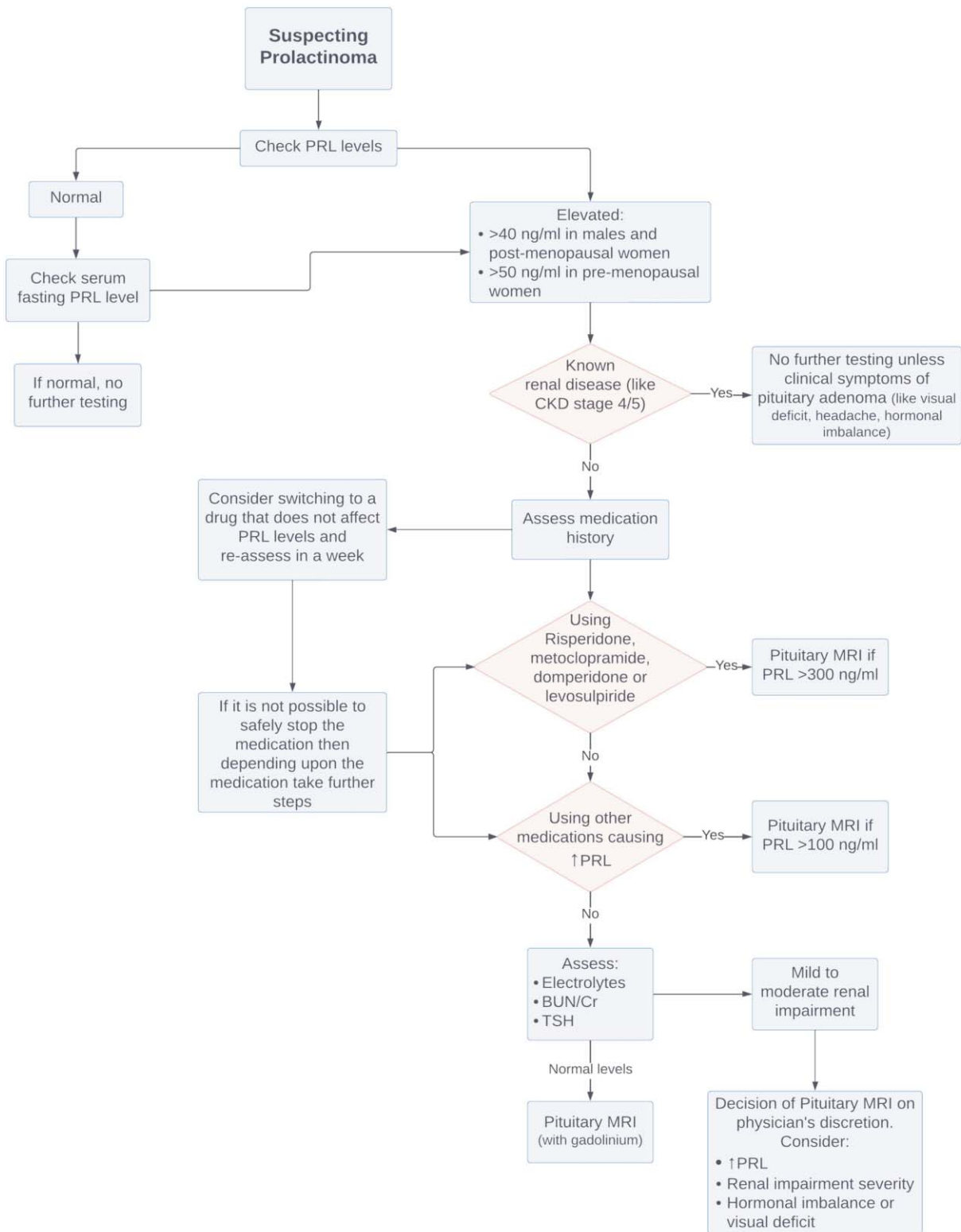


Figure-1: Work-up for a suspected prolactinoma.

periodically after starting medical treatment to assess response and improvement in visual field defects.^{10,12}

Recommendation 2.1: Offer medical treatment with Dopamine agonists (11) to patients with prolactinoma to normalize prolactin level, reduce tumour size and restore gonadal function (Figure 2)

Management: The treatment of prolactinoma is warranted for three primary reasons:

- 1- The presence of a large adenoma causing visual field defects or an imminent risk to the visual field, neurological symptoms, and hypogonadism. The significance of treatment increases with larger tumour sizes. Treatment becomes necessary when the tumour extends beyond the sella or affects the optic chiasm and adjacent structures.⁶
- 2- Symptomatic patients with hyperprolactinaemia present with galactorrhoea or hypogonadism.²
- 3- In women with regular menstrual cycles and mild hyperprolactinaemia who are attempting to conceive, treatment is advisable due to the potential occurrence of luteal phase defects that can lead to subfertility.¹⁰

Dopamine agonists: Dopamine agonists¹⁶ are effective in reducing the size of the majority of prolactinomas and lowering serum PRL levels. Consequently, they are widely recognized as the primary treatment option for managing hyperprolactinaemia, regardless of its cause or tumour size. These medications exert their effects by binding to dopamine receptors on the cell surface, leading to decreased PRL synthesis and release, as well as a reduction in the size of prolactinomas. Cabergoline is typically the preferred initial choice, with bromocriptine being considered as a secondary option.¹⁰

Recommendation 2.2: Offer medical treatment with cabergoline as a first-line treatment to patients with prolactinoma

Cabergoline is efficacious and has a satisfactory side effect profile. It is an ergot-derived DA prescribed once or twice a week and has a much lower propensity to trigger nausea than bromocriptine. It may also be effective in treating patients with bromocriptine-refractory prolactinomas.¹⁷

Even in patients with prolactinomas presenting visual field defects, Cabergoline can still be utilized as the primary treatment option, as long as the visual acuity is not at immediate risk due to rapid tumour growth or recent tumour haemorrhage.^{18,19}

The typical starting dose of cabergoline is 0.25 - 1 mg twice per week. Using such doses, PRL levels normalized in 61% of patients and were reduced by at least 75%.^{10,15,20}

Bromocriptine, an ergot derivative, has been employed for approximately three decades in the management of hyperprolactinaemia. For optimal therapeutic efficacy, it is typically administered two to three times a day. The typical starting dose is 1.25 - 2.5 mg orally at bedtime initially which may be increased by 2.5 mg/day every 2-7 days as per tolerance until optimal therapeutic response is achieved. The usual therapeutic dosage ranges from 2.5-15 mg/day in two to three divided doses. However, compared to cabergoline, bromocriptine is more prone to causing nausea as a side effect.^{5,9,12}

The initial six months following the initiation of DA therapy demonstrate the greatest reduction in PRL levels, with an average decrease of 86 ng/mL per month. In the subsequent six months, this reduction rate decreases to 7 ng/mL per month, and thereafter, it further declines to less than 1 ng/mL per month.^{19,21} Biochemical cure was achieved in 83.3% of patients treated with cabergoline, compared to 60.4% with bromocriptine.²⁰ The radiological response rates were 65.45% for the cabergoline group and 60% for the bromocriptine group.²⁰

Other Dopamine agonists: (the current guidance does not endorse the use of alternate DAs).

Pergolide: There are concerns about valvular heart disease with the use of this agent.

Quinagolide: This is reported to have comparable therapeutic effects to cabergoline in decreasing serum PRL and adenoma size. Its lack of availability in most countries makes its use infrequent.

Recommendation 2.3: Monitor for side effects of DAs

Typical: Commonly observed adverse effects of DAs include nausea, postural hypotension, and mental foginess. Less frequent side effects encompass nasal stuffiness, depression, Raynaud's phenomenon, alcohol intolerance, and constipation.¹²

Side effects tend to manifest when treatment is introduced or when the dosage is escalated. However, in most patients, these can be mitigated by commencing treatment with a small dose (e.g., half of the lowest strength bromocriptine pill once daily or half a cabergoline pill twice a week) and taking the medication

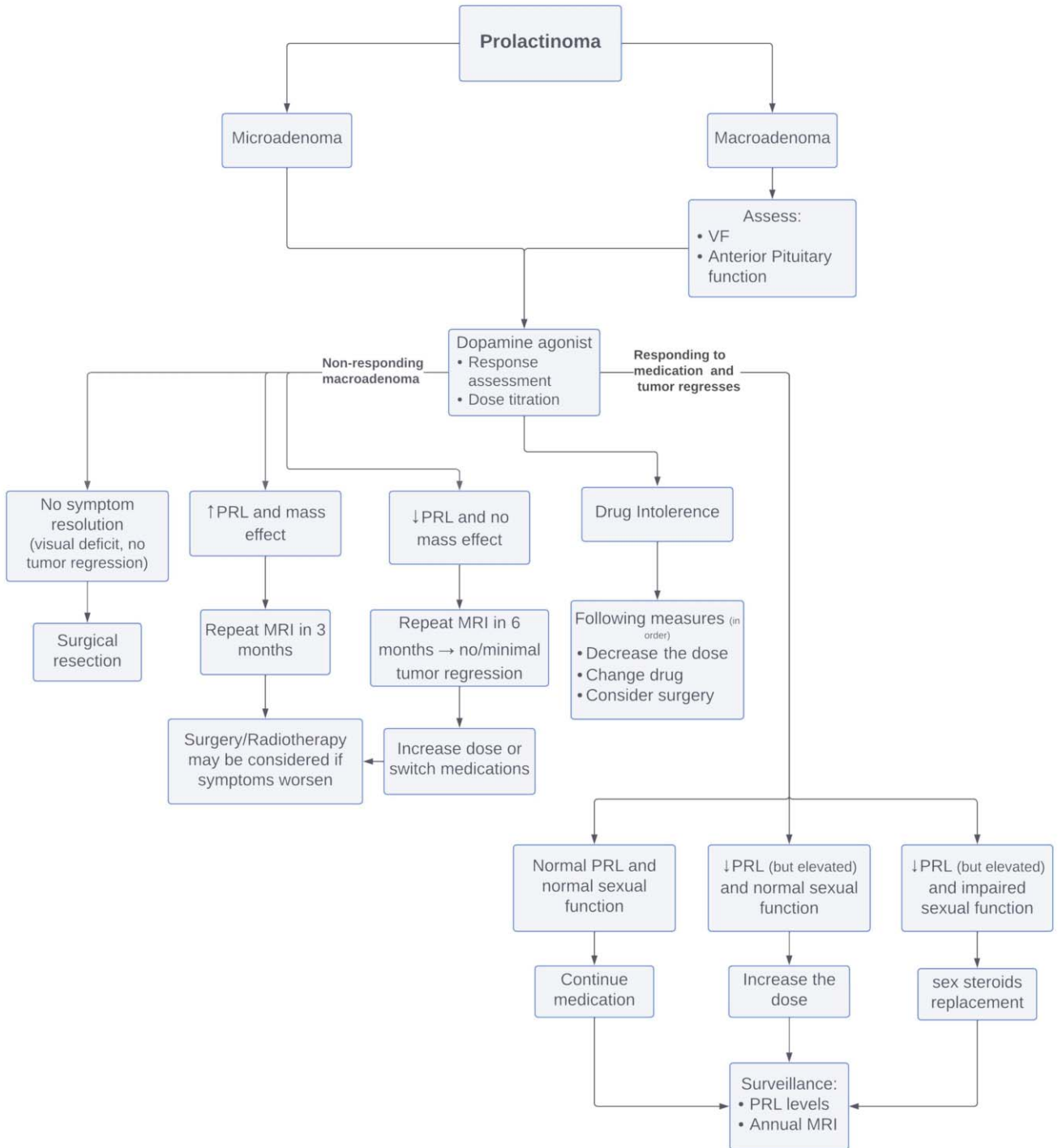


Figure-2: Management of Prolactinoma.

with food or at bedtime and then gradually building up the dose.²

Only a limited number of patients experience side effects, despite using the lowest doses. For women, the occurrence of nausea might be prevented by opting for intravaginal administration.¹⁰

Impulse control disorders — Impulse control disorders, although uncommon, are well-recognized side effects that may arise or worsen with DA treatment. These disorders can manifest as increased impulsivity in behaviours like hyper-sexuality, compulsive gambling, shopping, or eating.²²

Valvular heart disease: There is a reported association between cabergoline and pergolide usage and the development of valvular heart disease. The strength of this association appears to be dependent on the dosage of the medication.²³

Recommendation 2.4: Initiate DAs at the lowest dose and gradually up-titrate the dose to achieve normalisation or near-normalisation of prolactin level

Dose of DAs: Cabergoline should be started at a dose of 0.25 mg twice a week or 0.5 mg once a week. Giving the dose at dinner or bedtime reduces the chance of nausea or sleepiness.¹⁰

When initiating bromocriptine treatment, it is recommended to start with a dosage of 1.25 mg taken after dinner or at bedtime for one week. Subsequently, the dosage can be escalated to 1.25 mg taken twice a day, specifically after breakfast and after dinner or at bedtime.¹²

For macroprolactinomas, up-titration to higher doses may be needed depending upon the response of PRL level.²

Recommendation 2.5: Offer hormone replacement therapy (HRT) to women with macroprolactinomas who do not desire fertility and lack the symptoms of troublesome galactorrhoea

For women with micro prolactinomas who experience amenorrhoea but do not have bothersome galactorrhoea and are not seeking fertility, estradiol and progesterone replacement can be considered. These medications can be prescribed individually at low doses, similar to their use in treating hypogonadism of any cause. As an alternative option, oestrogen can be administered through a combined hormonal pill.¹⁰ It's crucial to

emphasize that oestradiol treatment bears a minor risk of prolactinoma enlargement, it is imperative to regularly assess serum PRL levels in patients undergoing this treatment.

Recommendation 2.6: Offer hormone replacement therapy in men with micro

prolactinomas who are intolerant or resistant to DAs and do not desire fertility and hCG treatment to those who desire fertility

For men with micro prolactinoma resulting in hypogonadism who are intolerant or resistant to DAs, testosterone treatment can be advised for those who do not desire fertility, and gonadotropins for those who want fertility.¹²

Recommendation 3.1: Consider trans-sphenoidal surgery for prolactinoma when there is resistance or intolerance to medical treatment (see text for further details) (Figure 2)

Micro prolactinoma: Transsphenoidal surgery (TSS) can be considered in patients with micro prolactinoma when:

- a) Despite undergoing DA treatment, the PRL concentration stays elevated.
- b) Symptoms or signs related to hyperprolactinaemia continue to persist even after many months of DA treatment on maximal tolerable doses.
- c) In situations where the patient is intolerant to DA and gonadal steroid replacement is not a viable option e.g. when pregnancy is desired.²⁴

Macroprolactinoma: Transsphenoidal surgery is usually reserved for patients with macroprolactinomas in the following situations:^{18, 25, 26}

- a) When there is compression of optic chiasma and visual deficits without rapid improvement with DA.
- b) In cases of resistance or intolerance to DA.²⁷
- c) When clinical manifestations of hyperprolactinaemia persist despite several months of DA treatment and gonadal steroid replacement is not feasible, such as when pregnancy is desired.²⁷
- d) For women with a giant lactotroph adenoma (e.g., >3 cm) who plan to conceive, trans-sphenoidal surgery (TSS) can be considered even if the adenoma responds to DA treatment. This approach is taken because if a patient becomes pregnant and withdraws

DA during pregnancy, there is a risk that the adenoma may increase in size to a clinically significant extent.^{27,28}

e) For giant pituitary tumours²⁹, it is critical to analyze tumour extension and location on the pre-operative imaging while selecting the surgical approach, as TSS (using an endoscope or microscope) alone may not provide optimal exposure. Depending on the tumour size, extension, and invasion cranial approach should be considered. In cases, with retrosellar or suprasellar extension or where the tumour is extending into the middle cranial fossa, a two-staged procedure, trans-sphenoidal followed by trans-cranial approach, can be used to ensure maximum removal of the tumour. The final approach selection is at the neurosurgeon's discretion.²⁹ (AKU-GPA paper reference)

Recommendation 4.1: Consider postoperative radiation therapy in patients with drug-resistant macroprolactinoma after surgical debulking (Figure 2)

Radiation (single dose or multiple fraction) is mainly reserved to thwart the re-growth of residual tumours in a patient with a huge macroprolactinoma after transsphenoidal debulking of prolactinomas which were resistant to cabergoline.^{18,26}

It should not be used for the primary treatment of prolactinomas.¹²

The decision of TSS or post-operative radiation therapy should be undertaken in a multidisciplinary meeting.¹⁰

Recommendation 5.1: Consider serial monitoring of patients on DAs through prolactin level

Follow-up after initiating DA:

- 1) Regular monitoring of PRL levels starting one month after initiating therapy, to adjust the dosage of DA to achieve normal PRL levels and restore normal gonadal function.¹⁰
- 2) In patients with microadenomas who achieve normo-prolactinaemia; PRL levels can be monitored 6 to 12 monthly.^{6, 10}

Recommendation 5.2: Perform serial assessment of visual fields through formal perimetry if there were evident initial visual field defects

Serial visual field examinations in patients with macroadenomas with baseline visual field defects. The decision needs to be individualized.

Recommendation 5.3: Obtain serial pituitary MRI in patients with macroprolactinoma for periodic monitoring.

The decision to conduct sequential imaging should be tailored to each case, taking into consideration various factors such as the size and invasiveness of the prolactinoma, treatment resistance, patient sex, oestrogen status, and previous treatments.

Consider performing MRI in 1 year or in 3 months in patients with macroprolactinoma, if:

- Continuous increase in PRL levels despite the patient receiving DAs.
- Development of new symptoms such as galactorrhoea, visual field defects, headaches, or other hormonal deficiencies.

Once maximum reduction in tumour size has been achieved, regular monitoring of PRL levels may be sufficient, and additional MRI scans may not be necessary.¹⁸

Recommendation 5.4: Manage comorbidities in patients undergoing treatment for prolactinoma

Management of comorbidities, e.g. sex-steroid-dependent bone loss, persistent galactorrhoea despite normalized PRL levels, and deficiencies in anterior pituitary hormones.

Recommendation 6.1: Offer DAs as initial treatment to patients with macroprolactinoma and visual field defects

Successful treatment with DA is depicted by a decreased PRL level and often rapid and progressive improvement of the visual impairment. DA improves the visual field by reducing the size of prolactinoma.^{10,18}

Recommendation 7.1: Consider withdrawal of DAs in patients who have achieved long-term normalization of prolactin level and the tumour size has reduced significantly (see text for further details)

Withdrawal of DAs: Tapering and discontinuing DA treatment, while ensuring normal PRL levels, can be considered in the following situations:¹⁸

Idiopathic hyperprolactinaemia (no pituitary mass at baseline): Serum PRL normalized on DA treatment and two years have passed.

Micro prolactinoma: Consider withdrawal of DAs if serum PRL normalized on DA treatment two years have passed

and there is no visible tumour on MRI. Discontinuation of dopamine agonists (DA) without prior withdrawal MRI can be contemplated for tumours with "favourable" characteristics, including small size, mild initial elevation of PRL levels, and longer duration of therapy. This approach is deemed safe and cost-effective.^{14,30}

Macroprolactinoma: Consider withdrawal of DAs if serum PRL normalized on DA treatment two years have passed and no visible tumour on MRI. In selected patients who have achieved normal PRL concentrations and >50% tumour size reduction, a careful withdrawal of DA can be considered keeping in mind the high risk of recurrence in this group of patients.^{10, 30,31}

Menopause: The risk of galactorrhea is very low after menopause due to the reduced oestrogen levels, making it feasible to attempt tapering and discontinuing DA treatment.³² DA withdrawal should not be attempted if the hyperprolactinaemia persists and a significant adenoma is still visible on MRI which is likely to increase the risk of adenoma progression.^{14,30}

Recommendation 7.2: Keep patients on periodic follow-up after withdrawal of DAs as there can be a risk of recurrence

The risk of recurrence of prolactinoma after DA withdrawal ranges from 26% to 69%.^{14,31} Recurrences are mostly expected within one year after DA withdrawal. Serum PRL should be measured every 3 months for the first year and if normo-prolactinaemia persists then it can be checked on an annual basis or earlier if symptoms recur. Pituitary MRI should only be offered if hyperprolactinaemia recurs.¹⁰

Recommendation 8.1: Get baseline and serial echocardiography in patients requiring long-term cabergoline at doses that are more than 2 mg per week

Monitoring of high-dose and long-term cabergoline use:

High doses of cabergoline i.e. more than 3mg/day for more than six months for the treatment of Parkinson's Disease may be associated with cardiac valvular defects.^{33,23}

We recommend monitoring as described below:³⁴

1. A baseline echocardiography should be obtained in patients with macroprolactinoma where high-dose cabergoline treatment is anticipated.
2. Patients receiving a weekly dose of cabergoline exceeding 2 mg must undergo annual echocardiography.

3. Patients receiving a weekly dose of cabergoline equal to or below 2 mg should have surveillance echocardiography at the 5-year mark. If any changes in valve function occur in these patients, annual echocardiography should be performed.

4. The decision to discontinue cabergoline should only be made after a thorough evaluation of serial echocardiography by an experienced physician who is knowledgeable about drug-induced valvopathy or carcinoid heart disease.

Recommendation 9.1: Manage resistant prolactinomas in tertiary care centres with the expertise and availability of a multidisciplinary team

Management for resistant prolactinomas: The available data indicates that DA treatment results in a more rapid decrease in PRL levels during the initial 6 months of therapy. Similarly, the most significant reduction in tumour volume during the first 6 months of DA treatment is observed at a rate of 3% of the initial volume per month, followed by a subsequent reduction of 0.5% of the initial volume per month ($P = 0.02$).²¹ Consequently, the tumour volumes reached a plateau at approximately 68.2% of the baseline volume by 12.6 months after the commencement of DA treatment.²¹

Resistant or refractory prolactinomas are resistant to DA.³⁵ Resistance is recognized when the PRL levels fail to normalize and reduction in the size of macroprolactinoma by 50% is not achieved on the maximum tolerated of DA (i.e. ≥ 2 mg per week dose of cabergoline and 15 mg/day of bromocriptine)¹⁰ Failure rates of 30% to 40% are reported with bromocriptine use and 10%-15% with cabergoline use.¹⁸

We recommend the following management of resistant prolactinomas:^{36,37}

- For patients on cabergoline without side effects, the dose can be increased to the maximum tolerated level. If the patient is on a different DA, they should be switched to cabergoline.
- TSS should be planned when medical treatment is unsuccessful and there is an increase in the tumour size;
- If surgery is unsuccessful then radiotherapy should be considered.
- Temozolomide may be a therapeutic option in malignant/aggressive prolactinomas.^{37,38}

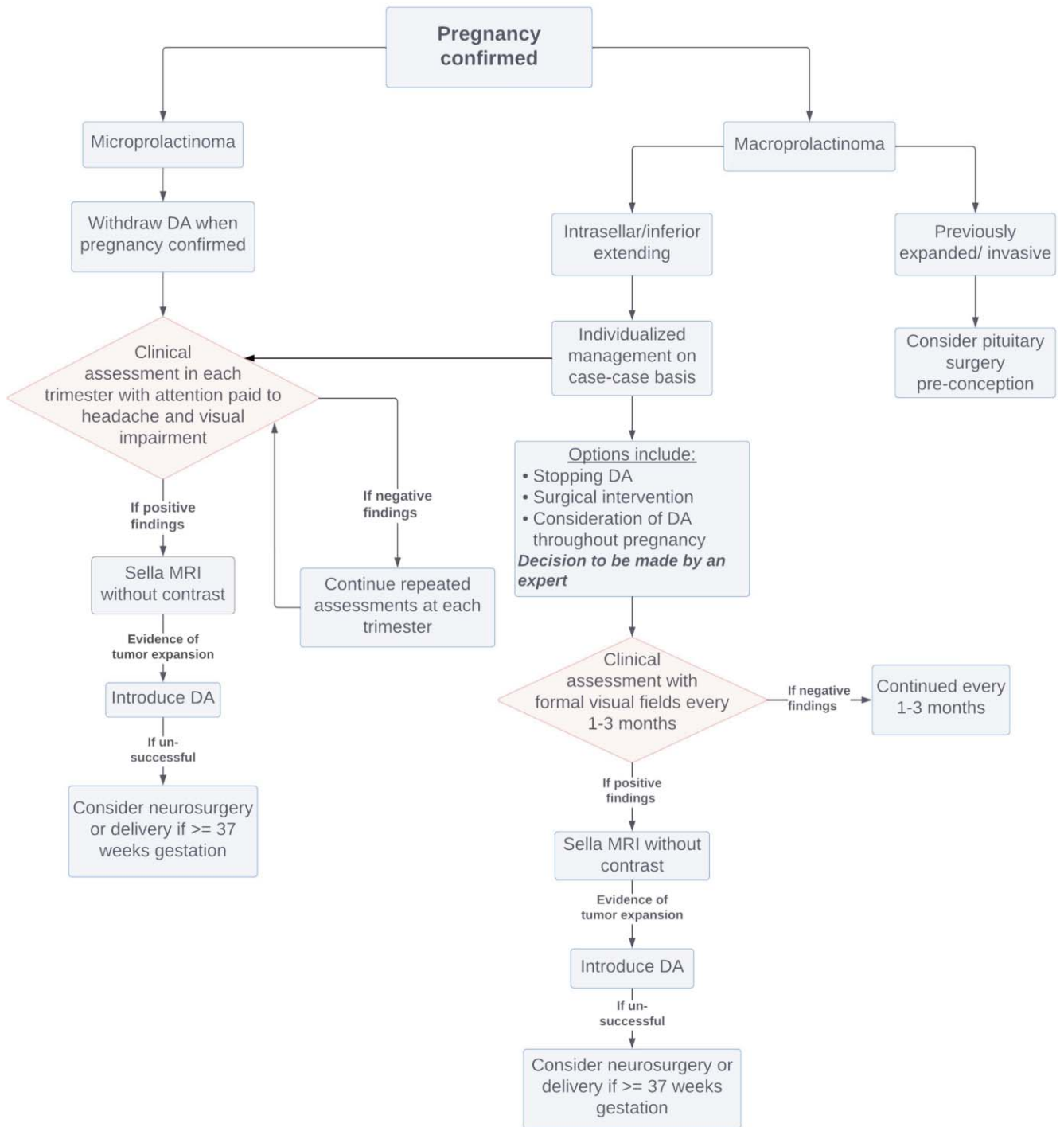


Figure-3: Management of prolactinoma during pregnancy.

Recommendation 10.1: Consider an individualized approach in managing women with prolactinoma anticipating pregnancy and during pregnancy. (see text for further details)

Prolactinoma and pregnancy:³⁹ In normal physiology, PRL levels gradually increase throughout gestation (approximately 10-fold), and then decrease after delivery in non-lactating women. Hyperprolactinaemia accounts for 7% to 20% of female subfertility cases. However, during pregnancy, hyperprolactinaemia does not impact the pregnancy itself or fetal development. However, there is a risk of estradiol receptor-related tumour expansion. The risk of symptomatic tumour enlargement is < 3% with microprolactinomas and 15-30% with macroprolactinomas.¹⁰ Since estimating PRL level is unreliable as a monitoring tool during pregnancy owing to the physiological increase in its levels, the reliance is mainly on clinical features of headache or visual field defects. Patients should be counselled to promptly report any new onset of headaches or visual defects. Owing to the higher likelihood of tumour growth potential with macroprolactinomas, formal perimetry is needed in each trimester. If there are any new visual field defects, then reinstating DA has to be considered, and if needed MRI pituitary (without gadolinium) can be offered after 16 weeks of gestation.

Microprolactinoma and pregnancy: (Figure 3)

Pregnancy should be deferred at least till the resumption of two normal menstrual cycles in women with microprolactinoma. Upon the onset of pregnancy, the DA should be discontinued, and the patient should be closely monitored for headaches or visual disturbances.⁴⁰

Macroprolactinoma and pregnancy: (Figure 3)

For macroprolactinomas, which have a high growth potential during pregnancy, it is crucial to allow sufficient time for dopamine agonists¹⁶ to reduce the tumour size before attempting to conceive. Pregnancy should be considered once the macroprolactinoma has shrunk and is confined within the Sella, away from the optic chiasma. If the woman is intolerant or resistant to DAs or wishes to conceive soon, TSS will be necessary. If a woman with a macroprolactinoma becomes pregnant and her tumour extends beyond the sella, DAs should be continued throughout the pregnancy.⁴¹ However, if the tumour is confined within the sella, the treatment approach should be individualized. The size of the prolactinoma dictates the need for pharmacological treatment during pregnancy, intending to keep the prolactinoma away from the optic chiasm. No increased risk has been

reported with either drug (bromocriptine or cabergoline) and long-term follow-up studies of children conceived while their mothers were taking these medications are also encouraging.^{18,42}

If there is expansion of a macroprolactinoma during pregnancy threatening vision, decisions regarding the reinstatement of DA in those who stopped at the onset of pregnancy, increasing the dose of DAs, or proceeding to TSS should be made through a multidisciplinary approach.

Discussion

The management of prolactinoma, especially in lower-middle-income countries (LMICs), requires a nuanced approach that balances efficacy, patient safety, and resource availability. Confirming hyperprolactinaemia is critical, particularly in equivocal cases, to avoid misdiagnosis and ensure appropriate treatment. It is equally important to rule out other causes of hyperprolactinaemia, such as medications, hypothyroidism, and renal insufficiency, to avoid unnecessary interventions. This diagnostic precision is essential to avoid unnecessary treatments and ensure that patients receive appropriate therapy from the outset.

Our recommendations emphasize the primary role of dopamine agonists¹⁶ such as cabergoline and bromocriptine in reducing prolactin levels and tumour size, aligning with global best practices.^{10,18} However, resistance or intolerance to DAs necessitates surgical intervention, specifically trans-sphenoidal surgery (TSS), which is effective in alleviating symptoms and controlling tumour growth in both micro- and macroprolactinomas.^{24,27}

Our guidelines reflect that the treatment approach must differ according to tumour size. For instance, microprolactinomas may primarily be managed with DAs, while macroprolactinomas might require a combination of medical, and surgical interventions and radiation therapy.¹⁸ Regular monitoring through prolactin levels, visual field assessments, and periodic MRI scans is essential for early detection of recurrence or treatment failure.⁶

Special attention is warranted for pregnant women with prolactinoma. Our recommendations prioritize pre-pregnancy tumour control and individualized monitoring during pregnancy to mitigate the risks of tumour expansion.³⁹ The management of resistant prolactinomas at specialised tertiary care centers ensures access to advanced treatments like temozolomide when conventional therapies fail.³⁷ Furthermore, the multidisciplinary

plinary approach ensures comprehensive patient care through collaborative decision-making, optimizing outcomes by leveraging diverse expertise.¹⁰

The management of prolactinomas, as outlined in our comprehensive guidelines, underscores the pivotal role of endocrinologists in ensuring accurate diagnosis and effective treatment. In LMICs, where healthcare resources may be constrained, our guidelines advocate for a multidisciplinary approach to prolactinoma management. The importance of specialized care in tertiary centres cannot be overstated, particularly for managing resistant prolactinomas or prolactinomas during pregnancy. Tertiary care facilities offer access to advanced therapies like temozolomide for aggressive tumours and provide comprehensive support through multidisciplinary teams. This approach not only enhances treatment outcomes but also ensures that patients receive personalised care tailored to their specific medical and reproductive needs. This collaborative model involves endocrinologists, neurosurgeons, radiologists, radiation oncologists, and obstetricians, among others, ensuring that patients benefit from a spectrum of expertise. Such coordinated care is particularly vital for complex cases or those requiring surgical intervention like trans-sphenoidal surgery (TSS), which is often the recourse for patients resistant or intolerant to dopamine agonists.¹⁶

Conclusion

The comprehensive management of prolactinomas, particularly in resource-limited settings, hinges on the effective use of medical and surgical interventions tailored to patient-specific needs. Dopamine agonists remain the cornerstone of treatment, with trans-sphenoidal surgery and postoperative radiation therapy providing vital options for resistant or intolerant cases. Regular monitoring and a multidisciplinary approach are critical to optimizing outcomes, ensuring timely intervention, and minimizing complications. Special considerations for pregnant women with prolactinoma highlight the need for individualised care plans to safeguard maternal and foetal health. Ultimately, adherence to these guidelines will enhance the quality of care for prolactinoma patients in LMICs, fostering improved long-term health outcomes and quality of life.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Cushing's Syndrome

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Introduction

Cushing's syndrome (CS) is caused by excessive cortisol production and is associated with significant morbidity and mortality.¹ Exogenous glucocorticoid (GC) therapy, including topical and inhaled corticosteroids, remains the most common cause of CS. Endogenous CS is traditionally divided into ACTH-dependent and ACTH-independent categories. (see Table 1)²

Table-1: Newel-price Jet al, Lancet 2006²

	Proportion	Female: Male
ACTH- Dependent		
Cushing's disease	70%	3.5:1
Ectopic ACTH syndrome	10%	1:1
Unknown source of ACTH	5%	5:1
ACTH - independent		
Adrenal adenoma	10%	4:1
Adrenal carcinoma	5%	1:1
Macronodular hyperplasia	<2%	1:1
Primary pigmented nodular adrenal disease	<2%	1:1
McCune -Albright Syndrome	<2%	1:1

Summary of recommendations

1. A detailed drug history should be taken to exclude the use of exogenous glucocorticoids, including topical or inhaled corticosteroids.
2. Biochemical confirmation of hypercortisolism is essential before initiating further investigations for the

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underlying cause of CS. These include

- Twenty-four-hour urinary free cortisol (at least two measurements) plus at least one of the following
- Overnight 1 mg Dexamethasone suppression test (1 mg DST)
- 48-hour low-dose dexamethasone suppression test (LDSST)
- Late-night salivary cortisol (two measurements)

3. After confirmation of endogenous hypercortisolism, it is recommended to measure fasting plasma corticotropin (ACTH) on two occasions
4. In ACTH-independent CS, cross-sectional imaging of the adrenal gland is recommended
5. In ACTH-dependent CS, a contrast-enhanced MRI Sella is recommended.
6. In ACTH-dependent CS, If an MRI scan shows a pituitary microadenoma >6 mm, surgical excision should be considered.
7. In patients without clear evidence of pituitary adenoma, production of excess pituitary ACTH should be confirmed with inferior petrosal vein sampling (IPSS).
8. If IPSS is not available or unsuccessful, the following tests are recommended to distinguish pituitary from non-pituitary causes of endogenous hypercortisolism:
 - Desmopressin or CRH stimulation test
 - High dose Dexamethasone suppression test
9. The optimal strategy for detecting non-pituitary ACTH-secreting tumours has not been defined. The available modalities include CT, MRI and PET scan (preferably ⁶⁸Ga DOTATATE PET/CT)
10. The first line treatment is trans-nasal, trans-sphenoidal resection of pituitary adenoma by an experienced neurosurgeon.

11. A post-operative MRI scan is recommended within 1-3 months of surgery.

12. We suggest a multidisciplinary approach regarding the use of second-line therapies which includes repeat transsphenoidal surgery radiotherapy, medical therapy and bilateral adrenalectomy.

Recommendations

Recommendation 1: Diagnostic Overview

In patients with high clinical suspicion for CS, further diagnostic workup should be conducted in a step-wise sequence as follows. See attached figure

Step 1: Confirmation of endogenous hypercortisolism

Step 2: Determine the underlying cause

*It is essential not to proceed to step 2 without completing step 1”.

Clinical suspicion

Endogenous CS is a rare entity. The reported incidence of pituitary ACTH-dependent Cushing’s disease, which accounts for 70% of endogenous CS, is reported to be between 3-6 cases/million/year.³

The most discriminatory clinical features for CS are facial plethora, proximal myopathy, skin thinning, cutaneous striae (red to purple and >1 cm), and excess bruising.^{4,5} In children, weight gain with reduced height percentile is pathognomonic of CS. Similarly, a young patient with a combination of hypertension, diabetes mellitus, or new-onset osteoporosis also warrants consideration of CS.⁶ Several other features commonly described in CS such as central adiposity, facial and supraclavicular fullness, hirsutism, acne, fatigue, or peripheral oedema are less specific (See Table 2).⁷

No single feature should prompt consideration of diagnosis for CS; however, a constellation of features, even if each is mild, should prompt a diagnostic workup. Routine screening for CS in at-risk populations, e.g., type 2 diabetes or obesity, is not recommended. (Table 2)⁷

Step 1: confirm endogenous hypercortisolism

In patients with suspected CS 24-h urinary free cortisol with at least one of the other tests outlined below should be conducted. In cases where clinical suspicion remains high but the results are borderline or one of the tests is normal, it is advisable to repeat the tests.

1. 24 hours Urinary Free Cortisol (2 measurements)
2. Overnight 1 mg Dexamethasone suppression test (1 mg DST)
3. Low dose Dexamethasone suppression test

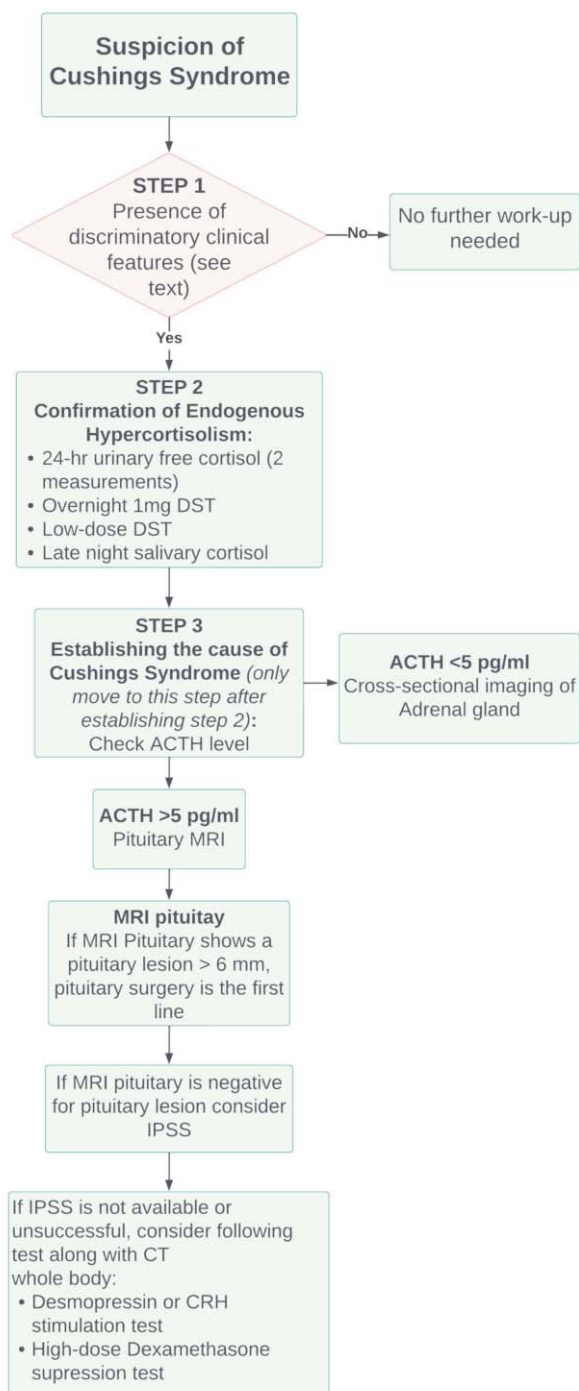


Figure-1: Algorithm for investigation of patient suspected to have Cushing syndrome.

(LDSST)

4. Late-night salivary cortisol (2 measurements)

Urinary free cortisol level (UFC)

UFC is the most widely used screening test for CS and

Table 2: JCEM pecori – Gerald F et al. 2003; 88:1554-1558⁷

Discriminatory	Less Discriminatory
<p>Signs</p> <ul style="list-style-type: none"> • Facial plethora • Proximal myopathy • Cutaneous striae • Excess bruising • Weight gain with reduced height percentile in the paediatric population <p>Symptoms and Complications (especially in younger adults)</p> <ul style="list-style-type: none"> • Hypertension • Diabetes Mellitus • Osteoporosis and vertebral fracture 	<ul style="list-style-type: none"> • Central adiposity • Dorsocervical hump/supraclavicular fullness • Facial fullness • Acne and hirsutism • Skin thinning • Poor wound healing • Peripheral oedema <p>Symptoms and complications</p> <ul style="list-style-type: none"> • Fatigue • Weight gain • Mental health abnormalities • Poor concentration and memory

directly assesses the circulating free cortisol. Free or unbound cortisol constitutes approximately 10% of the circulating cortisol and most of it is reabsorbed in the renal tubules.⁸ Excessive circulating cortisol saturates the binding protein, resulting in excess secretion of unbound cortisol.

The results can be affected by inappropriate sample collection. The correct method for collecting a 24-hour sample is to start collecting urine in the morning by discarding the first void and collecting all urine for the next 24 hours including the next morning's first void. Patients should avoid drinking excessive amounts of water during urine collection as high urine volume can result in falsely high 24-hour UFC.

False-positive UFC can be seen in many conditions, like depression, severe obesity, anxiety, and alcoholism. Many antibody-based immunoassays which are used for UFC measurement can give falsely high cortisol values due to cross-reactivity with cortisol metabolites. Similarly, drugs and compounds which inhibit 11 Beta HSD 2 like carbenoxolone, liquorice can also cause falsely high UFC

UFC can be falsely negative in mild CS; therefore two or more 24 hr UFC collections are recommended. Impaired renal function may also reduce UFC in patients with eGFR < 60, the sensitivity of UFC is greatly reduced.⁹

Late-night salivary cortisol (LNSC)

Salivary cortisol is in equilibrium with unbound plasma cortisol. It is independent of salivary flow rate and is stable in both room and refrigerator temperatures. The salivary cortisol measurement can be easily performed at home and it is a non-invasive test.¹⁰⁻¹² In suspected hypercortisolism, it is recommended to perform two late-night salivary cortisol measurements Elisa-based LNSC

assays tend to have variable reference values and a standard cut-off value has not been defined. Therefore, laboratory-specific cutoff values should be established.

Confounders include older age, hypertension, diabetes, smoking, variable bedtime, stress, liquorice, chewing tobacco, mild/ cyclical hypercortisolism

Dexamethasone Suppression Test¹¹

DST highlights the impaired feedback mechanism of the HPA axis which is the hallmark of CS. The overnight (1 mg DST) and 48-hrs dexamethasone suppression tests (2d DST) are widely used in conjunction with 2hH UFC.¹³

In the overnight DST, 1 mg of dexamethasone is administered at 2300 hours, and cortisol level is checked at 0800-0900 the following day. In standard low-dose 48-hour DST, 0.5 mg of dexamethasone is administered every 6 hours for 48 hours, starting at 0900 on the first day. The cortisol level is checked 6 hours after the last dose. The cutoff point for normal response is 1.8 micrograms/dL or 50 nmol/L after either test.^{9,13,14} (Table 3)

Several elements can be responsible for abnormal or altered dexamethasone suppression tests. The test can be affected by poor compliance with dexamethasone, or malabsorption, cp450 inducers like rifampicin, phenytoin, phenobarbitone, and alcohol can result in increased clearance thus reducing serum dexamethasone levels

Table-3: Dexamethasone suppression Test

Test	Dexamethasone dose	Measure Serum Cortisol
1 mg DST	1mg at 2300	Measure cortisol at 0800-0900
48H LDDST	0.5 mg 6 hourly for 48 hours	Last dose at 3 am, measure cortisol at 9 am

whereas liver or renal disease may lead to decreased clearance of dexamethasone hence leading to raised plasma levels.

In cases where the test is not in keeping with the clinical suspicion, it is recommended to measure cortisol and dexamethasone levels together. The expected levels of plasma dexamethasone should be >5.6 nmol/litre (0.22 $\mu\text{g/dl}$).¹⁵ However, this might not be feasible because of the limited availability and cost of the dexamethasone assay.

Other confounders for the DST include corticosteroid-binding globulin (CBG) abnormalities and cyclical hypercortisolism. CBG is increased in women taking oral contraceptive agents,^{16, 17} causing increased total serum cortisol. In such scenarios, either test should be repeated after holding oestrogen therapy for 6 weeks of using alternative tests.

Special situations

The following conditions can make the diagnosis of CS very challenging.

Cyclical CS –cyclicity might be revealed by doing multiple measurements of 24 hr urinary cortisol or bedtime salivary cortisol.

Renal failure (eGFR less than 60) – 1mg-ODST is recommended as UFC can be falsely negative.

In pregnancy or patients taking oral oestrogen therapy – DST may be falsely positive as oestrogen can increase serum total cortisol. UFC or salivary cortisol may be a better choice or the patient should stop oral oestrogen therapy for 6 weeks or change to topical oestrogen.

Step 2: Establishing the cause of CS

Once endogenous hypercortisolism is confirmed, the next step is to establish if it is ACTH-dependent or -- independent. This can be done by measuring fasting plasma corticotropin (ACTH) levels on two occasions. ACTH levels of <5 pg/ml indicate ACTH-independent CS, while levels above 15pg/ml are always due to ACTH-dependent pathologies such as pituitary adenoma or ectopic ACTH or corticotropin-releasing hormone [CRH] secretion.

Intermediate values may be seen in adrenal or pituitary pathology therefore cautious interpretation is required.¹⁸ ACTH is rapidly degraded by plasma protease. Blood for ACTH measurement should be collected in pre-chilled EDTA tubes, and it should be rapidly centrifuged and stored to avoid falsely low values due to the rapid degradation of ACTH by plasma protease

ACTH-independent CS

It is crucial to take a thorough history to exclude exogenous glucocorticoid intake. Once ACTH-independent CS has been confirmed, the next step is to obtain cross-sectional imaging of the adrenal gland. In the absence of a distinct adrenal lesion, consider primary pigmented nodular adrenal disease (PPNAD).

ACTH-dependent Cushing syndrome

In ACTH-dependent CS the main challenge is to differentiate between pituitary and non-pituitary cause of CS. A contrast-enhanced sella MRI is the preferred imaging modality and a CT scan is not recommended. Dynamic MRI or spoiled gradient recalled acquisition MRI techniques provide slightly greater sensitivity than conventional MRI but have more false-positive scans.^{19,20} As there is a 10% chance of finding pituitary incidentalomas in the normal population²¹, a biochemical confirmation of ACTH-dependent CS must be undertaken before proceeding to pituitary imaging.

Once the biochemical diagnosis of ACTH-dependent CS is confirmed and an MRI scan shows a definitive lesion >6 mm, pituitary surgery is recommended. In the absence of a definitive lesion on MRI bilateral inferior petrosal vein sampling (IPSS) should be undertaken to differentiate the pituitary from the nonpituitary cause of ACTH-dependent cortisol excess.²²

Inferior Petrosal Sinus Sampling IPSS

IPSS is associated with significant morbidity; therefore, the test should only be conducted in an expert centre. The procedure included the placement of catheters into the inferior petrosal sinuses which drain the pituitary. The inferior petrosal sinus ACTH levels are compared with the peripheral ACTH sample taken simultaneously before and after intravenous administration of CRH or desmopressin.^{23,24}

A basal ratio central to peripheral (C:P) ratio $> 2:1$ or post-stimulation ratio of $>3:1$ is diagnostic of pituitary ACTH production.²⁵ The sensitivity and specificity of IPSS is 94% (22). Prolactin measurement may improve diagnostic accuracy and it is best to draw prolactin with each ACTH draw and process the sample if the ACTH levels ratio is borderline. A baseline C:P prolactin ratio of >1.8 has been suggested as confirmation of a successful catheterization.²⁶

The sensitivity and specificity of IPSS is 94%.²² If a gradient is present, surgery can be considered even if the MRI pituitary is negative depending upon the consensus of a multidisciplinary team (MDT).

In one series a combined approach using CRH /desmopressin stimulation, MRI, followed by whole-body CT, correctly diagnosed CD in approximately half of the patients in the absence of IPSS.²⁷

CRH stimulation test

CRH test is used to differentiate pituitary origin ACTH dependent CS from ectopic ACTH-secreting tumours. ACTH-producing adenomas tend to abundantly express CRH receptors and thus respond to CRH with exuberant ACTH production as opposed to ectopic ACTH tumours which exhibit minimal response to intravenous CRH administration.^{28,29}

Nieman et al. reported that with bovine CRH, a 35% increase in ACTH was associated with 100% sensitivity and 93% specificity, whereas a 20% increase in cortisol gave 91% sensitivity and 88% specificity.³⁰

CRH is not available in Pakistan.

Desmopressin (DDAVP) stimulation test

Desmopressin stimulates ACTH secretion similar to that of CRH and when given to patients with pituitary origin ACTH dependent has a comparable response to CRH,³¹ although some 20% of patients do not respond to DDAVP.²⁹

High Dose Dexamethasone suppression test

The high-dose dexamethasone suppression tests are used to differentiate between pituitary and non-pituitary origin ACTH-dependent CS. The test is done either as a 48-hour test in which 2 mg dexamethasone is given every 6 hours for 48 hours or an overnight test where a single 8 mg oral dose of dexamethasone is given at 2300 hrs and serum cortisol is measured between 0800 to 0900 the following morning. The principle behind the high-dose dexamethasone suppression test is that overproduction of ACTH observed in ACTH-producing pituitary tumours, but not the ectopic tumours, can undergo partial or complete suppression by high-dose dexamethasone.

Management

First-line treatment

The first line treatment option for Cushing disease is trans-sphenoidal resection of pituitary adenoma by an experienced pituitary surgeon

3.1.1 Peri-operative care:

Glucocorticoid therapy

Stress dose peri-operative glucocorticoid therapy is required in patients

taking adrenal blockade therapy with adrenal enzyme

inhibitors to avoid adrenal crisis. In patients not taking adrenal blockade therapy, routine glucocorticoid therapy may not be warranted.

To avoid the symptoms of acute steroid withdrawal, steroids are given for 1-3 days post-operatively, either dexamethasone 0.5 mg every six hours for 24 hours or hydrocortisone 50 mg every 6 hours for 24 hours.

To assess remission after surgery, glucocorticoids need to be stopped for 24 hours before serum cortisol can be measured. During this period the patient must be carefully monitored for features of adrenal insufficiency. Serum cortisol must be checked and if morning cortisol >9 µg/dL (250 nmol/L) then glucocorticoid therapy is not required but if <9 µg/dL (250 mol/L) then it should be given and the patient retested at a later date

Patients who have achieved remission will become hypo adrenal and will require physiological glucocorticoid replacement until there is evidence of HPA axis recovery.

It is noteworthy that in patients with a history of severe hypercortisolism, symptoms of acute steroid withdrawal can occur when taking 'physiological' replacement therapy. These patients might benefit from higher doses of glucocorticoids (i.e. double dose) followed by a slow taper to standard replacement dose.

All patients with CD who are receiving physiological glucocorticoids should be counselled about stress doses of steroids during intercurrent illness or a surgical procedure and should be given steroid-alert bracelets/cards

Electrolytes and other Monitoring

During the first 2 weeks post transsphenoidal surgery sodium level should be measured regularly. Within 1-2 weeks, Free T4 levels should be checked for overt hypothyroidism. Within 1-3 months, a post-operative MRI scan should be done

3.1.2 Remission after TSS

Remission is defined as:

1. Morning serum cortisol values <5 µg/dL (<138 nmol/L) or
2. UFC < 28 –56 nmol/d (<10 –20 µg/d)

within 1 week of selective tumour resection.

The rate of remission is higher in patients with smaller, non-invasive adenoma, tumours with pre-operative 24- hr Urinary cortisol less than 1250 nmol/L and postoperative serum cortisol < 2 µg/dL (< 55 nmol/L)^{26,28}

3.2.3 Medical Management of Cushing Syndrome

Medical management is indicated in the following:

- Preparation for surgery
- Unwilling or unfit to undergo surgery
- Post-pituitary radiotherapy to control symptoms of hypercortisolism while waiting for the effect of the pituitary radiation field.²⁹
- Treatment of ectopic ACTH syndrome.
- In patients with acute and life-threatening hypercortisolism complications such as sepsis, severe hyperglycaemia, uncontrolled hypertension, heart failure, intractable hypokalaemia, and psychosis.

Pharmaceutical agents such as Ketoconazole, metyrapone, Osilodrostat and Mitotane inhibit the synthesis and secretion of cortisol. Of these, only Ketoconazole is currently available in Pakistan. The dose of ketoconazole is 400 to 1200 mg per day and it leads to a greater than 50% drop in UFC in 75% of 200 patients along with clinical improvement in hypertension, diabetes, and hyperkalaemia.³²

Ketoconazole can cause gastrointestinal disturbances, reversible hepatotoxicity, gynecomastia, skin rash, and adrenal insufficiency. Idiosyncratic severe hepatic dyscrasia is estimated to occur in one in 15,000 individuals taking ketoconazole.^{30,31} Hence Liver function tests need to be performed before the initiation of ketoconazole and it should not be started if the patient has a liver disease with alanine aminotransferase levels more than three times the normal upper range. On the other hand, those Patients who have elevated values but levels are below 3 times the normal upper range usually have cortisol-induced non-alcoholic hepatosteatosis which will improve with ketoconazole treatment. Ketoconazole can prolong the QT interval; thus, concomitant administration of other agents that also prolong the QT interval is contraindicated. The efficacy of ketoconazole is decreased in the presence of antacid therapy.

Other medical treatments such as Somatostatin receptor ligand³³ and Dopamine agonists (Cabergoline) are ACTH-directed agents which decrease pituitary ACTH production. Cabergoline is used in milder hypercortisolism.³⁴ Pasireotide, a somatostatin analogue that binds to somatostatin receptors thus blocking the release of ACTH from the corticotroph. It is currently not available in Pakistan.

Mifepristone a glucocorticoid receptor antagonist is used for the treatment of patients who have Cushing

syndrome as well as diabetes or glucose intolerance and are not surgical candidates or have failed surgery.^{29,34,35} Mifepristone blocks cortisol receptors, hence the ACTH and cortisol levels rise and the dose is adjusted based on clinical parameters like weight, blood pressure, glucose levels and other phenotypic features of hypercortisolism. Mifepristone is available in Pakistan.

Long term Follow-up Monitoring for Recurrence

Cushing disease CS patients need lifelong surveillance for recurrence with at least 6-12 monthly assessments for 5 years and then less frequently. The monitoring can be considered earlier if patients report any reappearance of symptoms of CD; a situation in which they should be encouraged to contact their healthcare team sooner.

Reevaluation should include:

- 24-hour urinary cortisol, and/or
- 1 mg dexamethasone suppression test
- Late-night salivary cortisol

Evaluation for bone and skeletal health

Patients should be monitored for bone health which tends to improve over time with normalisation of cortisol levels.

Risk of atherosclerotic cardiovascular disease (ASCVD):

Patients with controlled CS continue to have a higher risk of ASCVD secondary to insulin resistance residual visceral obesity and dyslipidaemia. The high-risk features need identification and control as appropriate.

Psychological support

Throughout the disease management course, additional psychological intervention should be offered based on patient needs.

Treatment if surgery fails

A review of pathology results should be undertaken if there is a persistent biochemically proven disease after surgery. If a tumour is not found on the histopathology, then the initial diagnosis should be revisited for differential diagnosis, the possibility of ectopic CS, and the need for additional testing.

Therapeutic options for persistent disease:

- Repeat surgery – should be considered if Sella MRI shows a residual tumour. However, the success rate of repeat surgery is inferior to initial surgery and also increases the risk of hypopituitarism.
- Pituitary gland irradiation – stereotactic

radiosurgery/radiotherapy

- Medical therapy.
- Adrenalectomy – Medical or surgical.
 - o Medical adrenalectomy with mitotane, for example, may be used in conjunction with pituitary irradiation
 - o Surgical adrenalectomy

Discussion

The diagnosis and management of CS remains a considerable challenge. Cortisol can affect virtually every cell in the body, therefore the clinical features due to CS are widespread and overlap with multiple other conditions. Endogenous CS is rare, and hence it is crucial to avoid over-diagnosing the condition.

This guideline focuses on the diagnosis and management of Cushing syndrome in developing countries like Pakistan. The additional challenge is non-availability of biochemical investigation like salivary cortisol. CRH and Intravenous desmopressin are not available in Pakistan. Very limited centres in Pakistan are conducting IPSS. Regarding Medical management of Cushing syndrome, only Fluconazole and Mifepristone are available in Pakistan.

Conclusion

This guideline aims to streamline the diagnostic and management step with available resources.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Thyrotropinoma (TSHOMA)

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Introduction

TSHoma, thyroid-stimulating hormone-secreting pituitary adenoma is one of the rarest pituitary adenomas having a prevalence of 0.5–2%.¹ These tumours are characterised by high levels of circulating free thyroid hormones (FT4 and FT3) along with raised serum TSH concentration.² Most TSHomas are diagnosed in the fifth or sixth decades,³ with equal prevalence in men and women.¹ The main differential diagnosis of this biochemical feature is thyroid hormone resistance.²

Summary of recommendations

1. If TSH is elevated while FT3 and FT4 are also elevated, TSHoma should be considered as a potential diagnosis.
2. A close differential of thyroid hormone resistance should be considered.
3. A repeat test in 1 month needs to be done to rule out any interfering factor
4. Family screening for thyroid profile needs to be done.
5. MRI pituitary should be done to look for pituitary adenoma
6. Functional testing like Pet Scans etc. can be done.
7. Dynamic testing is recommended internationally to differentiate between the TSHoma and RTH. The only test which we recommend is the

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somatostatin suppression test depending on availability of the somatostatin analogues.

8. Surgical treatment is recommended as first-line therapy.
9. The patient should be made euthyroid before surgery with somatostatin analogues or antithyroid drugs
10. Long-acting somatostatin analogues and radiotherapy are the second and third-line therapy
11. There is no exact criteria for cure but a euthyroid state is recommended, normal hormone profile, and improved neurological symptoms should be considered as a cure.
12. Follow-up should be twice in the first year and then annually.
13. Follow-up should include a thyroid profile. MRI pituitary should be done every 2-3 years

Recommendations

Recommendation 1: clinical presentation

Presenting complaints in descending order include¹

- Goiter,
- Signs and symptoms of thyrotoxicosis,
- Visual symptoms,
- Headache,
- Multiple pituitary hormone deficiencies
- Galactorrhea.

Clinical features of hyperthyroidism are sometimes milder and do not reflect the level of FT3, FT4, and TSH hormones.² It is either, the compressive symptoms like headache, visual defects, etc, or the other pituitary hormonal deficiency results in consultation with a specialist and cranial imaging.

Recommendation 2: investigations

Hormonal: The hallmark of diagnosing TSHoma is the raised FT4 and FT3 with high TSH levels.³ Repeat sampling along with antithyroid antibodies at 1 month time from another laboratory should be done to exclude interference by medication, pregnancy oestrogen, non-thyroidal illness, and autoimmune thyroiditis.⁴

As TSHoma can be a co-secretory pituitary adenoma for growth hormone and prolactin hence IgF1 and Prolactin levels should be done. Cortisol and gonadotrophin levels can be low and should be evaluated. Hyperthyroidism due to RTH can be differentiated from TSHoma by doing carboxy-terminal cross-linked telopeptides of type-I collagen (ITCP). It will be raised TSHoma elaborating the excessive effect of thyroid hormone in the bone. Due to the mutation of TR β in the case of RTH bone will be spared of this effect,⁵ not routinely recommended due to the cost constraints and unavailability.

Thyroid hormone testing in first-degree relatives needs to be done to rule out RTH. α subunit can also be measured as it is raised in 30% of the patients with TSHoma depending on its availability.⁵

Radiological**• Structural Imaging**

MRI of the pituitary gland shows macro-adenomas in the anterior pituitary in about 80% of patients.² A negative MR imaging may mean a microadenoma that cannot be visualized.² Ectopic tumours are usually found in the pharyngeal region.⁶

• Functional imaging

Scintigraphy: Scintigraphy with radio-labelled octreotide can be used to localize most hormone-producing adenomas as they have high numbers of somatostatin receptors.⁷

1. Position Emission Tomography: Pituitary microadenomas which are missed by MRI can be detected by using PET/CT. For ectopic TSH-producing adenoma gallium-labelled somatostatin receptor analogues (⁶⁸Ga-DOTANOC, DOTATATE, DOTATOC) have been evaluated in a small number of case series with successful results.⁸

Dynamic testing

As most of these tests are not available in Pakistan. We are mentioning them however we do not recommend them. (Figure 1)

1. TRH Stimulatory test

The stimulatory test is done by giving TRH (200 μ g bolus

intravenously, sampling done at 0, 20, 60, 90, and 120 min). A rise of more than 50% or a rise in TSH of more than 4iu/l is considered normal. In the case of TSHoma, the response is blunted in 90% of patients however an exaggerated increase is seen in patients with RTH⁶.

A Stimulated alpha subunit (α SU) is a 100% increase after TRH administration and is positive in 44% of cases.⁶

2. T3 Inhibitory test

This inhibitory test includes administration of T3 (80–100 μ g/day, divided into 3 administrations for 10 days, sampling at 0, 5, and 10 days) leading to complete suppression of the TSH. However, in Tshoma complete suppression was never seen.⁶

Indications²

1. Blunted response to TRH test with no pituitary lesion on MRI.
2. A normal response to TRH in the presence of a pituitary adenoma,
3. Previous thyroidectomy
4. Rule out hyperplasia/adenomas in the pituitary from RTH

Contraindications²

1. Cardiopulmonary disease
2. Psychiatric disease
3. Any disease which will lead to decompensation from a short period of hyperthyroidism.

2. Somatostatin suppression test

This test can be performed especially in patients with microadenoma. It will help in differentiating incidentaloma from TSHoma as well as the main differential of RTH. Chronic administration of long-acting somatostatin analogues (20–30 mg i.m. every 28 days for 2–4 months, sampling at 0 and every 28 days just before the new injection) in patients with central hyperthyroidism caused a marked decrease of free T4 and free T3 levels.⁷ (Table 1)

Recommendation 3: treatment**Surgical treatment**

First-line treatment is either transsphenoidal or sub-frontal adenectomy. Complete removal is possible in microadenoma but there is 60% complete resection in macroadenoma. Patients need to be prepared and made euthyroid before surgery. Antithyroid drugs like methimazole and carbimazole or somatostatin analogues like octreotide and lanreotide are used.^{9,10}

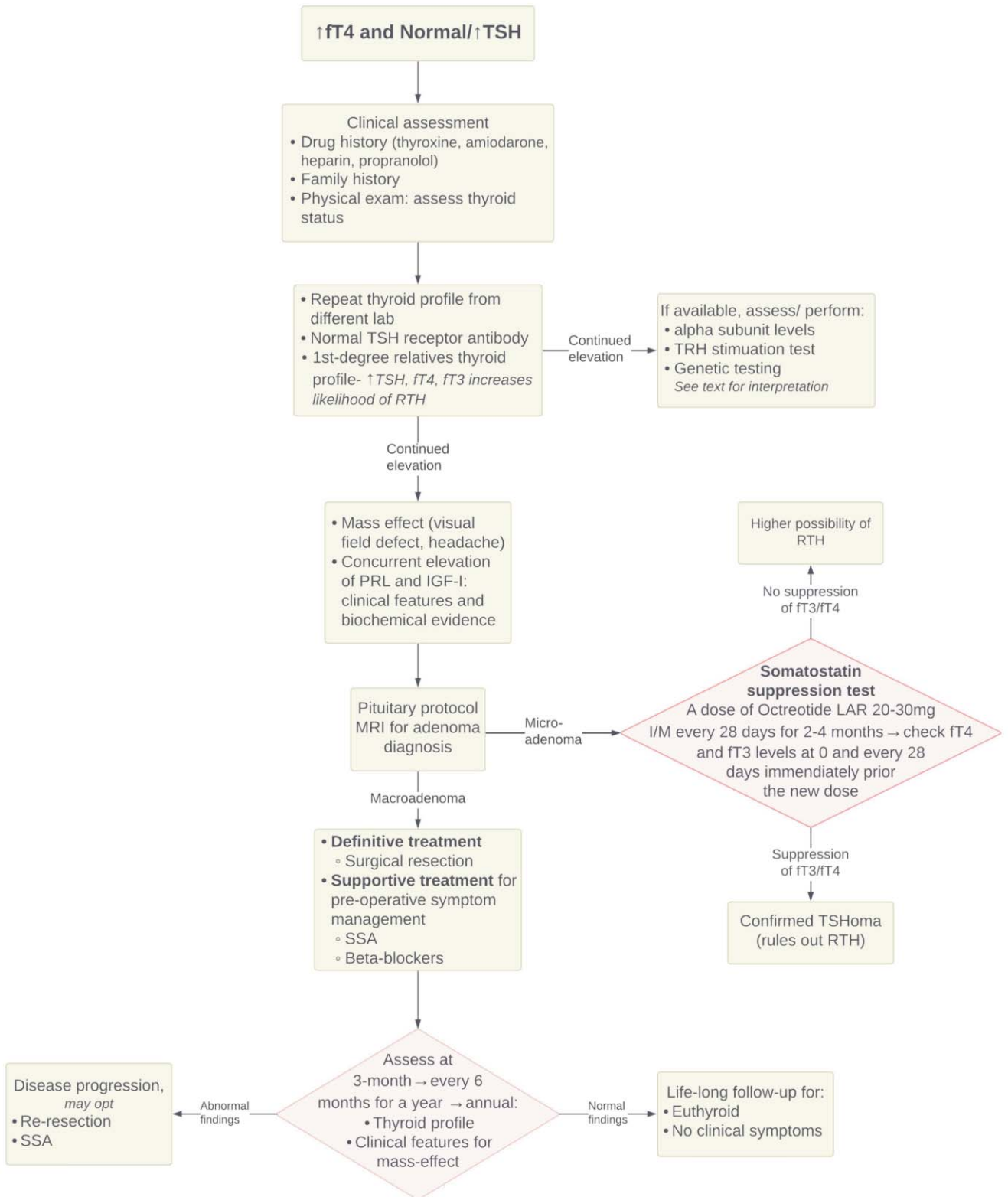


Figure: Diagnosis and Treatment of TSHOMA

Table-1: Comparison of TSHoma and RTH

Clinical features/test results	TSHoma	RTH
<i>Clinical features</i>		
Goiter	Present	Present
Visual field	Affected	Normal
<i>Blood works</i>		
Pituitary hormonal disturbances	Present	Absent
Alpha subunit (aSU)	Raised	Normal
<i>Imaging</i>		
Pituitary MRI	Adenoma	Normal/hyperplasia
<i>Stimulation tests</i>		
TRH stimulation test	Blunted response	Exaggerated response
Rise in alpha subunit (aSU)	Rises	No response
<i>Suppression tests</i>		
T3 suppression test	TSH not suppressed	TSH suppressed
Somatostatin suppression test	FT4 decreases by >30%	No effect
<i>Genetics</i>		
DNA mutation	None	Present
<i>Invasive tests</i>		
Sinus petrosal sampling	Elevated	Normal

TRH- thyrotropin releasing hormone, TSH- thyroid stimulating hormone, FT4 free levothyroxine, DNA- deoxyribonucleic acid, MRI-magnetic resonance imaging,

Medical therapy

Somatostatin analogues: Somatostatin analogues are recommended for medical therapy for TSHoma. Long-acting somatostatin analogues, that is octreotide LAR, and lanreotide SR result in a reduction in both α -SU levels in all the cases, leading to euthyroid status in most of the patients.⁶

Somatostatin analogues lead to the normalisation of Circulating thyroid hormone levels in more than 90% of patients and a significant reduction in goiter size in about 30% of cases. Significant pituitary adenoma shrinkage is observed in about 40% of patients and 70% have shown improvement in visual field defects.¹⁰

Dopamine agonist: As dopamine receptors are present in TSHoma, Bromocriptine, and Cabergoline have been used with partial response.

Radiation therapy

Pituitary fractionated stereotactic radiotherapy or radiosurgery is considered when surgical and medical therapy is either contraindicated or declined.¹¹

Recommendation 4: cure

There are no established criteria for a cure. However, euthyroid status improvement of neurological symptoms and normalization of the thyroid hormone levels can indicate the success of the surgical procedure or radiotherapy.

Recommendation 5: follow-up (Figure 1)

The patient should be evaluated at 3 months and 6 monthly for a year post-op and then annually. Follow-up should include TSH and FT3, FT4. Other pituitary hormones should be evaluated if indicated. Repeat Pituitary imaging should be done every 2 -3 years. Immediate Pituitary imaging should be done if TSH levels rise, or the patient develops neurological symptoms. In case of a residual macroadenoma, close follow-up of visual fields should be performed.¹¹

Discussion

While autoimmune diseases and toxic goitres are common culprits behind hyperthyroidism, a much rarer cause exists - TSH-secreting pituitary adenomas (TSHomas). Unlike typical hyperthyroidism, TSHomas present a unique picture: high levels of free T3 and free T4 alongside non-suppressed levels of TSH.²

The main challenge lies in differentiating TSHomas from another condition called Resistance to Thyroid Hormone. Ideally, specific tests involving stimulation and suppression of TSH, along with genetic analysis, would be used for clear diagnosis. However, the limitations and unavailability of these tests can make it difficult to reach a definitive conclusion.⁶

These guidelines propose alternative approaches to navigate the diagnostic challenge:

- Family History:** Screening the patient's first-degree relatives by checking their thyroid profile can provide valuable clues.
- Pituitary Function Assessment:** Checking other pituitary hormone levels helps assess overall pituitary function, potentially revealing abnormalities.
- Pituitary Imaging:** If imaging techniques like MRI scans reveal a pituitary adenoma (especially a large one – macroadenoma), it strengthens the suspicion of TSHoma.
- Somatostatin Analogue Test (Treatment and Confirmation):** Administering somatostatin analogues, which are medications used to treat TSHomas, can serve a dual purpose. If FT3 and FT4 levels are suppressed after 2-4 doses, it further supports the diagnosis and simultaneously prepares the patient for definitive treatment – surgery.

Conclusion

These guidelines offer a practical approach to diagnosing TSHomas when traditional testing methods are

unavailable. By combining family history, pituitary function assessment, imaging, and a therapeutic trial with somatostatin analogues, doctors can achieve a more accurate diagnosis and guide patients toward the best course of treatment.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Functioning Gonadotroph Adenoma

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Introduction

The functioning gonadotroph adenomas (FGAs) are the pituitary tumours that initiate production of active gonadotropins. Among the confirmation of gonadotroph adenomas through the immunohistochemical method, it is studied that the vast majority of tumours are hormonally inactive and merely present with physical effects.¹ From a surgical point of view, these hormonally silent adenomas constitute about 64% of the clinically nonfunctioning pituitary adenomas.²

FGAs constitute a minor percentage of tumours affecting humans presenting mainly with irregular menses and OHS in females and adolescent girls having perimenopause, enlarged testis in males, and isosexual precocious puberty in children.¹ Consequently, FGAs are supposed to be considered when there is a presence of high testosterone/oestrogen levels and standard or elevated follicle-stimulating hormone (FSH)/luteinizing hormone (LH).³

Summary of recommendations

1. Consider the early diagnosis of Functional Gonadotropin Adenomas (FGAs) in patients presenting with sellar mass, particularly in premenopausal females and adolescent girls who exhibit menstrual irregularity and ovarian hyperstimulation syndrome (OHS), males with testicular enlargement, and children with isosexual precocious puberty.
2. The primary therapeutic approach for FGA is

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surgical excision, which, when successful, leads to the restoration of regular gonadotropin secretion and alleviation of symptoms.

3. Adjuvant radiotherapy may be considered following partial resection if repeat surgery is not feasible.
4. Medical interventions including somatostatin analogues, GnRH agonists and dopamine agonists are employed in selected patients, but they are generally not recommended as the primary treatment approach.

Recommendations

Recommendation 1: Diagnosis

FGA presents by means of sellar mass, following symptoms and biochemical findings.

1.1 In men, the clinical presentation often includes hypogonadism, testicular enlargement, and also symptoms such as headaches and visual deterioration. Biochemically, their serum FSH levels are typically elevated, whereas the levels of testosterone and serum LH may drop in comparison to the reference range to some extent, within the standard range, or may be elevated. Serum alpha subunit and inhibin levels tend to be normal or elevated, and there is often an increased sperm count.

1.2 In Premenopausal Women, irregular menses (oligo-/amenorrhoea, menorrhagia), ovarian hyperstimulation syndrome, galactorrhoea, infertility, and mass effects such as headaches and visual deterioration. Biochemically, there is evidence of hyperoestrogenism, although occasionally oestrogen levels may be within the normal range or show fluctuations. Serum FSH levels are typically within the specified reference range or might be slightly elevated. The serum LH levels are often lower or within the reference range. Furthermore, the serum levels of alpha-subunit and inhibin tend to be standard or raised.

1.3 Diagnosis of FGA in post-menopause women is

challenging due to the misinterpretation of elevated gonadotropin levels as a natural consequence of menopause, coupled with the absence of clinical symptoms, as the ovaries are no longer sensitive to FSH.

1.4 In children, FGA may present with symptoms of isosexual precocious puberty, including mass effects, elevated serum FSH levels, abnormal serum LH levels, and increased oestradiol in females or testosterone in males.

1.5 An elevated response of FSH, LH, and LH-beta to thyrotropin-releasing hormone (TRH) in both males and females may be observed. This is considered in the context of a sellar mass, assuming there is no history of primary hypogonadism.

Recommendation 2: Surgical Treatment

The primary treatment for adenoma is surgical removal, which, if successful, results in the restoration of normal gonadotropin secretion.⁴ In women, this procedure is the prime solution of ovarian hyperstimulation syndrome with a reduced ovary size along with regularity in menstrual cycles.⁵ In males, after complete resection, there is a reduction or normalization of FSH and inhibin levels, as well as a decrease in testicular volume.⁶

Recommendation 3: Adjuvant Radiotherapy

Adjuvant radiotherapy can be considered after partial resection if repeat surgery is not possible. Studies and data on long-term follow-ups are not available. If there are cases of regrowth in the tumour, radiotherapy treatments are selected as the treatment option.⁶

Recommendation 4: Medical Therapy

The medical interventions involve the use of dopamine agonists,⁷ GnRH agonists, somatostatin analogues, including antagonists in selected cases. However, it is important to note that these treatments have not been linked to tumour shrinkage, and as a result, they are generally not recommended as the primary therapeutic approach.¹

Follow-Up

The long-term clinical and imaging follow-up is essential due to the risk of recurrence. Comprehensive long-term data regarding patient outcomes following surgery, with or without radiotherapy are currently lacking. The literature contains reports of both stable tumour appearances with no clinical recurrence and instances of tumour regrowth accompanied by the recurrence of clinical symptoms.

Discussion

Gonadotroph adenomas are considered hormonally silent tumours, however in some rare cases, they can

present with clinical symptoms related to gonadotropin secretion.^{1,8} The clinical manifestation presented by this adenoma is gonadal disturbance which usually causes menstrual irregularities in premenopausal females, isosexual precocious puberty in children and enlargement of testes in males. However, published literature on FGAs primarily consist of small cases series and reports, resulting in a lack of calculated prevalence of this rare entity.¹ This guideline aims to address the diagnosis and management of FGAs specifically within the context of low- and middle-income countries (LMICs) such as Pakistan, where access to extensive data and resources may be limited.

The guidelines recommend that the early diagnosis of FGAs should be considered in patients with sellar mass accompanied by the presence of elevated testosterone/oestrogen and normal or elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Early diagnosis leads to better outcome.³ The primary treatment for adenoma is surgical removal, which, if successful, results in the restoration of normal gonadotropin secretion.⁴

The medical interventions involve the use of dopamine agonists, GnRH agonists, somatostatin analogues, including antagonists in selected cases.

Conclusion

Despite the limited availability of data on Functional Gonadotroph Adenomas (FGAs), this guideline seeks to offer practical recommendations for the management of this rare condition. Given the rarity of FGAs and the challenges associated with their diagnosis and treatment, we have compiled evidence-based strategies and expert opinions to guide clinicians in the effective management of these tumours. Our goal is to provide a framework that addresses the unique aspects of FGAs, from diagnosis to treatment, while acknowledging the need for further research to refine and enhance these recommendations.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Pituitary Adenoma - Stereotactic Radiosurgery

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Introduction

Pituitary adenomas present a challenging treatment scenario, as microsurgery alone often falls short of a cure. These tumours frequently demand a multifaceted approach, encompassing surgical intervention, radiation therapy, radiosurgery, and medical management.

The benchmark for treating both symptomatic non-secreting and secreting pituitary adenomas, excluding prolactinomas, is surgical resection, which achieves a control rate ranging from 50% to 80%.¹

Radiotherapy for pituitary adenomas has seen advancements over time, delivering precise and well-tolerated treatment with excellent outcomes. It administers a dose of radiation that halts or destroys tumour cells without exceeding the radiation tolerance of surrounding healthy tissues.

Summary of recommendations

- 1- Stereotactic radiosurgery (SRS) is recommended for residual, relapsed and surgically contraindicated cases.
- 2- SRS achieves early radiological and biochemical control compared with conventional radiotherapy.
- 3- Maximal debulking surgery should be done in functional cases before SRS to achieve early remission.
- 4- Anti secretory medicines should be stopped 6 to 8 weeks before SRS and should be started after SRS.
- 5- SRS doses to critical regions should be respected and mentioned in discharged documents.

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Conventional radiation therapy

Initially, radiotherapy involved two-dimensional, parallel-opposed fields or minimally blocked bitemporal fields. Today, it has evolved into three-dimensional or Intensity-Modulated Radiotherapy (IMRT) with computer tomographic assistance. This approach employs multiple fields, custom blocks, or Multileaf Collimation to concentrate therapeutic doses while minimising risks to normal tissues. Current conventional radiotherapy typically employs doses of approximately 45-50 Gy, delivered in daily fractions of 1.8 Gy.²

Conventional radiotherapy, when used alone, attains tumour control rates of around 80-85% at ten-year follow-ups.³ However, for functional pituitary adenomas, the long-term biochemical remission rate remains low at 38-40%.⁴

Due to these facts nowadays, conventional radiotherapy serves as a treatment option in regions where Stereotactic Radiosurgery (SRS) is unavailable or when SRS is not feasible, such as due to non-visualization or severe compression of the optic chiasm.

Stereotactic Radiosurgery (SRS):

SRS is a newer technique for radiotherapy in pituitary adenoma cases. SRS delivers highly focussed radiation with sub-millimetre precision, targetting the tumour while sparing nearby structures. Stereotactic image guidance ensures accuracy. SRS is typically administered in a single fraction but may also be given in 3 or 5 fractions depending on various parameters.⁵

Radio surgical treatment worldwide is given by different technologies, including Gamma Knife, CyberKnife, Novalis, True Beam STX, and Axesse, as well as proton beam units like IBA or Mevion.

SRS achieves tumour control rates ranging from 83% to 100%. Hormone normalisation through SRS takes longer than surgery but less time than conventional radiation therapy. The remission timeframe varies from 3 months to 8 years, with Cushing's disease showing the highest rates, followed by acromegaly, prolactinomas, and Nelson's syndrome.

Volume effect of adenomas. It has been observed that patients who had a lower adenoma volume being treated by radiosurgery had early endocrine remission. Thus, for functional adenomas maximal debulking surgery should be done before SRS treatment.⁶

For Cushing's disease, remission rates after SRS range from 17% to 87%, with the average remission rate exceeding 50%. Neurological deficits occur at a rate of 3.4%, and hypopituitarism at 23%.

For acromegaly, SRS achieves an average endocrine remission rate of 61%, ranging from 0% to 82%. Neurological deficits are seen in 1.8% of cases, and hypopituitarism in 14.7%.

For prolactinomas, the average endocrine remission rate after SRS is 29%, ranging from 0% to 83%. Neurological deficits occur in 3.5% of cases and hypopituitarism in 15%.⁷⁻⁹

Proton therapy has emerged as a tool for intracranial radiosurgery, benefitting from the superior dose distribution of protons compared to photons, thanks to the Bragg peak phenomenon through which there is a reduction in beam entry and exit dose. The absorbed dose while passing ultimately rises to its maximum in the region of pathology and then abruptly stops, Bragg peak occurs exactly within the tumour site. However, only a few centres currently employ proton beam technology for radiosurgery.¹⁰

Recommendations

Indications of SRS

1. Apoplexy, 1st option is surgery, if progressive/recurrent/residual/excess hormone levels after surgery, then 2nd option may be **SRS**.

2. Micro /Macroadenoma, 1st option is surgery, if progressive/recurrent/residual/excess hormone after surgery, then 2nd option may be **SRS**.

3. Cavernous Sinus Invasion, 1st option is SRS, if progressive/recurrent/residual/excess hormone after SRS, then repeat **SRS**.

4. Unsuitable for Surgery / Refusing Surgery / Patients Choice then consider **SRS**.

5. Unsuitable for Surgery / SRS (Non-Visualization / Severe Optic Chiasm compression) then EBRT preferably IMRT.

Anti-secretory medication for acromegaly/prolactinomas, if used during SRS will lead to poor endocrine remission results as they lower the radio

sensitivity and also reduce the DNA damage during SRS.¹¹ Pakistan pituitary adenoma guidelines committee recommend stopping all these medications 6 to 8 weeks before SRS. After SRS, patients are transitioned to suppressive medications and periodically assessed for treatment results. Pakistan pituitary adenoma guidelines committee suggest the continuation of these suppressive medications for six months post-SRS and then two months of drug holiday and later check hormonal levels, this practice should continue till normalisation of excess hormones is achieved.^{11,12}

Radiosurgery doses. It is mandatory to respect the threshold and maximum point dose to the optic pathway in SRS and doses to all critical organs should be provided to patients for future reference.

Single fraction SRS doses for nonfunctioning adenomas range from 12 to 18 Gy and 15 to 30 Gy for functioning adenomas and 3 to 5 fraction SRS dose range from 21 to 25 Gy for nonfunctional adenomas and 24 to 30 Gy for functional adenomas.

Adverse events following radiosurgery for pituitary adenomas are relatively rare but can include:

Hypopituitarism, the most common adverse event, 30 % of patients may develop single or multiple hormone deficiencies during their follow-up evaluations. It mainly affects anterior pituitary hormones and less posterior pituitary hormones, panhypopituitarism is a very rare occurrence. The risk of hypopituitarism is influenced by various factors, including the state of the pituitary gland before radiosurgery, the effect of previous surgeries, and the dose delivered to the gland. In the literature, there exists no safe SRS dose to avoid this complication.¹³

- 1- Clinical Evaluation and pituitary hormone assessment should begin one year after pituitary radiation and re-assessment should be done annually until at least 10 years following radiation.¹⁴
- 2- To assess ACTH deficiency 9 AM cortisol should be checked. TSH deficiency can be checked by monitoring Free T4. Growth hormone deficiency can be assessed by checking IGF-1 levels. However, IGF-1 should be assessed only in patients who are good candidates for growth hormone replacement. FSH/LH deficiency can be monitored by checking morning testosterone in males. FSH, LH and oestradiol can be checked in females if they develop secondary amenorrhoea.

2- Cranial nerve damage, SRS may lead to damage to cranial nerves lying in the para cavernous region i.e. 11,

111, 1V, and V1 cranial nerves.¹⁵

3-Radiation necrosis of adjacent parenchyma, and

4- Internal carotid artery narrowing.

5-Radiation-induced secondary malignancies¹⁶

Discussion

The management of adenomas involves a multidisciplinary approach. For prolactinomas, medical treatment is the primary modality, with further intervention only if refractory. In contrast, surgery is the gold standard for nonfunctional and functional adenomas, with residual or recurrent disease managed through stereotactic radiosurgery (SRS). SRS is also used as the primary treatment when surgery is contraindicated due to medical conditions, patient refusal, or critical tumour locations.

A study treated 41 post-surgical residual ACTH-secreting adenomas with single-fraction SRS, achieving a 60.97% biochemical remission at 14 months without visual deterioration over a median follow-up of 48.8 months.¹⁷ Another study found that 12.2% of GH-secreting adenomas achieved biochemical remission post-SRS, with some patients requiring further medical treatment.¹⁸ Overall, SRS provides a viable treatment option with manageable side effects for adenomas when surgery is not suitable.

Conclusion

SRS is effective in the treatment of pituitary adenomas characterized by high rates of local control and endocrinological remissions with minimal toxicity.

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Pakistan Endocrine Society (PES) and Pakistan Society of Neuro-Oncology (PASNO) guidelines 2024 for the management of Preoperative Endocrine Management of Pituitary Adenoma

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Introduction

Patients undergoing trans-sphenoidal surgery for pituitary adenomas require careful perioperative care due to the delicate nature of the pituitary function and the risks of complications during the postoperative period. The diagnoses that usually require specific perioperative consideration are acromegaly, Cushing's disease, and macro or giant adenomas with compression of the optic apparatus. The most common complications after transsphenoidal surgery include hyponatraemia, hypopituitarism, CSF leak, and epistaxis.^{1,2} Patients require careful monitoring for these problems, and institutional protocols for perioperative care can help limit these adversities.³ All patients with pituitary adenomas need a thorough endocrinological evaluation in the pre-operative period and follow-up in the post-operative period, especially, given the need for hormone replacement therapy.

Summary Of Recommendations

1. Serum Prolactin and IGF-1 should be measured in all cases of pituitary adenoma
2. Patients with pituitary macroadenoma should undergo evaluation for secondary adrenal insufficiency (AI) preoperatively.
3. All patients with pituitary adenoma, who show any symptoms or signs of cortisol excess, should be evaluated for Cushing's syndrome preoperatively.
4. Thyroid functions should be tested in all patients with pituitary tumours, preoperatively.

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5. Gonadal functions should be assessed preoperatively in patients with large pituitary mass (>1cm) or having symptoms of hypogonadism.
6. Patients with pituitary mass should be evaluated for diabetes insipidus if they have polyuria or hypernatraemia.
7. Patients with secondary AI should be given glucocorticoid replacement preoperatively.
8. Patients with secondary hypothyroidism should receive thyroxine replacement preoperatively.
9. Perioperative stress dose glucocorticoid administration is recommended in patients with known or suspected AI.
10. Serum sodium should be monitored postoperatively as sodium abnormalities can occur after pituitary resection. Central DI can cause hypernatraemia and hyponatraemia may occur due to a syndrome of inappropriate ADH secretion, cerebral salt wasting, or hypocortisolism.
11. In patients who do not have secondary adrenal insufficiency preoperatively, serum cortisol should be measured at 8 to 9 am postoperatively on days 1 to 5. A cortisol level < 3 ug/dL (83 nmol/l) is indicative of AI and a cortisol level > 15 ug/dL (415 nmol/l) likely excludes an AI diagnosis.
12. Complete pituitary hormonal evaluation should be done at 6 – 12 weeks postoperatively.
13. Dynamic testing to assess the HPA-axis should be done at 6-12 weeks after surgery if morning serum cortisol seems insufficient in the early postoperative period.
14. Biochemical testing for the HPA-axis is done at least 18 –24 hours after the last hydrocortisone dose or longer for synthetic glucocorticoids
15. Morning serum growth hormone may be measured on day 1 or 2 after surgery to assess remission in

patients with acromegaly.

16. Serum IGF-1 should be checked at 6 weeks postoperatively to see endocrine remission in acromegaly. If it remains elevated, it should be re-evaluated at 12 weeks to decide persistent disease.
17. In Cushing's disease, post-surgical morning serum cortisol (between 8 and 9 am) is used to assess remission after pituitary surgery. Remission is likely for values < 5 µg/dl (138 nmol/l).
18. Desmopressin may be used as required in the postoperative period if the patient develops cranial diabetes insipidus after pituitary surgery.

Recommendations

Preoperative Assessment of Pituitary Function

1. Serum Prolactin should be measured in all cases of pituitary adenoma
2. Patients with pituitary macroadenoma, who have minimally elevated serum prolactin should be tested for prolactin levels in serial dilutions, to nullify the hook effect.
3. Serum IGF-1 should be measured in all patients with pituitary tumours.
4. Patients with pituitary macroadenoma should undergo evaluation for secondary adrenal insufficiency (AI) preoperatively.
5. Patients with pituitary tumours, who present with manifestations of AI, should be evaluated for adrenal reserve pre-operatively, regardless of the size of the lesion.
6. All patients with pituitary adenoma, who show any symptoms or signs of cortisol excess, should be evaluated for Cushing's syndrome pre-operatively.
7. Patients with an apparent clinically non-functioning pituitary adenoma may be evaluated for Cushing's disease pre-operatively.
8. Thyroid functions should be tested in all patients with pituitary tumours, pre-operatively.
9. Gonadal functions should be assessed pre-operatively in patients:
 - a. Who present with symptoms of hypogonadism.
 - b. Who show a large pituitary mass (>1cm).
 - c. Who have a functioning pituitary tumour, regardless of the size.

10. Patients with pituitary mass should be evaluated for diabetes insipidus if they have polyuria or hypernatraemia.

Pre-operative Hormone Replacement and Medical Management

11. Patients with secondary AI should be given glucocorticoid replacement preoperatively.
12. Patients with secondary hypothyroidism should receive thyroxine replacement preoperatively.
13. Perioperative stress dose glucocorticoid administration is recommended in patients with known or suspected AI.
14. The stress dose glucocorticoid is, Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h IV or IM)
15. In patients with growth hormone-secreting tumours, pre-operative medical management with somatostatin receptor ligands can be considered in selected patients.
16. In patients with ACTH-secreting pituitary adenoma, pre-operative medical management can be considered in selected cases.

Postoperative Endocrine Assessment

17. Serum sodium should be monitored post-operatively as sodium abnormalities can occur after pituitary resection. Central DI can cause hypernatraemia and hyponatraemia may occur due to a syndrome of inappropriate ADH secretion, cerebral salt wasting, or hypocortisolism.
18. In patients who do not have secondary adrenal insufficiency preoperatively, serum cortisol should be measured at 8 to 9 am postoperatively on days 1 to 5. A cortisol level < 3 µg/dL (83 nmol/l) is indicative of AI and a cortisol level > 15 µg/dL (415 nmol/l) likely excludes an AI diagnosis.
19. Complete pituitary hormonal evaluation should be done at 6 – 12 weeks post-operatively.
20. Serum prolactin may be measured post-operatively on day 1 or 2, to evaluate for remission in patients with prolactin-secreting tumours.
21. Dynamic testing to assess the HPA-axis should be done at 6-12 weeks after surgery if morning serum cortisol seems insufficient in the early postoperative

period.

22. Biochemical testing for the HPA-axis is done at least 18 –24 hours after the last hydrocortisone dose or longer for synthetic glucocorticoids
23. Thyroid function should be assessed in all patients at 6 – 8 weeks after pituitary surgery.
24. Serum-free T4 (fT4) and TSH are measured to evaluate thyroid status. An fT4 level below the reference range in association with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms a secondary hypothyroidism diagnosis.
25. The gonadal function should be evaluated at 6 – 12 weeks postoperatively, in men and premenopausal women.
26. Dynamic testing may be done to assess pituitary growth hormone reserve postoperatively, in patients suspected to have growth hormone deficiency.

Patients with Acromegaly

27. Morning serum growth hormone may be measured on day 1 or 2 after surgery to assess remission in patients with acromegaly.
28. Serum IGF-1 should be checked at 6 weeks postoperatively to see endocrine remission in acromegaly. If it remains elevated, it should be re-evaluated at 12 weeks to decide persistent disease.
29. A glucose tolerance test for growth hormone suppression may be carried out to confirm endocrine remission in acromegaly, after several weeks of surgery.

Patients with Cushing's disease

30. Post-surgical morning serum cortisol (between 8 to 9 am) is used to assess remission after pituitary surgery
 - a. It is usually performed 1–7 days after surgery (before morning glucocorticoid administration)
 - b. Remission is very likely for values < 1.8 µg/dl (50 nmol/l)
 - c. Remission is likely for values < 5 µg/dl (138 nmol/l)
 - d. Persistent disease is likely for values > 7.2 µg/dl (200 nmol/l)
31. Twenty-four hours of urine-free cortisol measurement may be used to assess biochemical remission.

32. Late-night salivary cortisol measurement can also be used to assess remission.

Postoperative Hormone Replacement

33. Desmopressin may be used as required in the postoperative period if the patient develops cranial diabetes insipidus after pituitary surgery.
34. In post-pituitary surgery DI, the clinicians should make at least one attempt to discontinue DDAVP during the weeks/months after surgery to determine whether posterior pituitary function has recovered.
35. In cases of adipsic DI, DDAVP, and fluid intake titration should be done carefully by frequent weighing and serum sodium level monitoring.

Discussion

Measuring serum prolactin is necessary in all cases of pituitary adenomas, as it is the most common hypersecretion from a pituitary tumour.⁴ Prolactin immunoassays may not correctly detect very high levels of hormone in the serum, due to the "hook effect", so a prolactin-secreting tumour may be misinterpreted as a non-functional pituitary adenoma, greatly affecting the management decision.^{5,6} So, serum prolactin levels may be checked in dilutions in patients with macroadenomas.⁷ Serum IGF-1 should be checked pre-operatively in all patients with pituitary tumours because growth hormone-secreting tumours do not always present with classic manifestations of acromegaly.⁸ A retrospective observational study of 37 patients with NFPAs, who underwent trans-sphenoidal surgery revealed that 19(51%) patients showed positivity for GH immunostaining despite a lack of clinical suspicion for acromegaly. Three (8.1%) of these patients had slightly elevated IGF-1 levels. The authors recommended that pre-operative laboratory assessment for NFPAs should include an IGF-1 level.⁹ Mild hypercortisolism may be more common than generally thought. Typical signs and symptoms of cortisol excess may not be present in ACTH-secreting tumours presenting as pituitary incidentalomas.⁹ Silent corticotroph adenomas are a subtype of nonfunctioning pituitary adenomas (NFPAs) which have positive immunohistochemistry for ACTH without showing any clinical signs of cortisol excess. They are biologically aggressive tumours and retrospective analysis of these patients showed that many of them had high preoperative ACTH levels. Some of these cases can be diagnosed by preoperative testing for hypercortisolism.^{10,11} About 50% of cases of central hypothyroidism are associated with pituitary macroadenomas.¹² The frequency of central

hypothyroidism with NFPAs may be up to 43% preoperatively and 57% postoperatively.¹³ Preoperative assessment of gonadal functions with morning FSH, LH and sex steroids (estradiol and testosterone) is recommended in all patients with pituitary tumours because hypogonadism and GH hormone deficiency are the commonest found disorders with pituitary tumours.¹⁴ Sex steroid replacement is not recommended preoperatively because it carries a prothrombotic risk during the perioperative period.¹⁵ Patients with polyuria (more than 50 mL/kg of body weight/24 hours, 3.5 L/d in a 70-kg person) and high serum osmolality (> 295 mOsmol/L) with urine osmolality less than 600 mOsmol/L (urine osmolality/plasma osmolality ratio should be >2), must be evaluated for DI preoperatively.¹⁶

Patients with secondary AI and hypothyroidism should be optimally replaced preoperatively. The recommended daily dose of hydrocortisone is 15 – 20 mg in 2 or 3 divided doses, with the highest dose taken in the morning on rising. Longer-acting glucocorticoids can be used in selected cases, due to non-availability or poor compliance. Levothyroxine is adjusted in a dose to keep the free T4 level between the mid to upper level of the reference range.¹⁶ Stress doses of glucocorticoid replacement are the same as in primary adrenal insufficiency.¹⁷ Primary medical therapy with a somatostatin receptor ligand (SRL) may be considered in selected patients with macroadenomas without local mass effects on the optic chiasm, as SRLs have been shown to reduce tumour size and control GH hypersecretion. However, the evidence is yet insufficient to support the general use of an SRL before surgery to improve post-surgery biochemical outcomes.¹⁸ Preoperative medical treatment for Cushing's syndrome can be considered in selected patients. Data from the European registry ERCUSYN showed that 20% of patients received preoperative medical treatment mainly Metyrapone and/or ketoconazole. There was no difference in remission rate or morbidity after six months based on whether preoperative medical treatment was given or not.¹⁹ On the other hand, preoperative medical management can be considered in patients who have severe Cushing's syndrome or who are not fit for surgery because of comorbidities due to hypercortisolism.^{20,21}

Serum sodium levels should be monitored for approximately 7–10 days postoperatively. The incidence of postoperative hyponatraemia can be as high as 20%, and sometimes it can be a part of triphasic response.^{16,23} Symptomatic hyponatraemia may occur in up to 5% of cases.¹⁶ Transient and permanent DI can occur in up to 4.3% and 0.3% of cases, respectively.²³ Euvolaemic

hyponatraemia may result from SIADH, while hypovolaemic hyponatraemia is caused by CSW. The management of SIADH after pituitary surgery constitutes a period of careful observation, followed by free water restriction if the hyponatraemia persists. CSW is managed by fluid repletion with normal saline and oral salt replacement. In refractory cases, fludrocortisone may be used with monitoring for hypokalaemia, fluid overload, and hypertension.²⁴ Postoperative morning cortisol below 3 ug/dl suggests AI and above 15 ug/dl excludes AI. For values of morning cortisol between 3 and 15 ug/dl, a corticotropin stimulation test is performed 6 – 12 weeks after surgery. Peak cortisol levels < 18.1 g/dL (500 nmol/L) at 30 or 60 minutes indicate AI.¹⁶ Serum-free T4 level below the reference range and TSH at low, normal or slightly higher levels indicates secondary hypothyroidism. In patients with pituitary disease and low-normal FT4 levels suspected to have mild secondary hypothyroidism, levothyroxine can be started if suggestive symptoms are present or following free T4 levels over time and starting treatment if the free T4 level decreases by 20% or more.¹⁶ The development of AI after pituitary surgery is a sign of disease remission. Morning serum cortisol is the most commonly employed test to ascertain Cushing's disease remission, but late-night salivary cortisol, 24-hour urine-free cortisol and DDAVP provocation testing are also used.²⁵⁻²⁷

Postoperative DI may be transient or permanent. Transient DI occurs within 24–48 hours after surgery and improves in the next few days. It is probably due to mild and reversible injury to the pituitary stalk or posterior pituitary lobe.²⁸ Permanent DI occurs when the hypothalamus and/or pituitary stalk are irreversibly damaged. Postoperative DI can occur in combination with an episode of SIADH. It happens when injured cells of the hypothalamic-pituitary tract release all stored vasopressin. It usually occurs 5–8 days postoperatively. Patients on desmopressin due to preceding DI may develop hyponatraemia when this SIADH develops. In the biphasic pattern, normal fluid balance is restored after the episode of SIADH (DI-SIADH-normal fluid homeostasis). In case no restoration to the posterior pituitary tract has occurred, the typical, but rare, triphasic pattern occurs and permanent DI will occur (DI-SIADH-DI).²⁹ Adipsic DI occurs in patients with thirst impairment. It is very rare and is caused by hypothalamic damage due to extensive surgery in patients with large tumours or craniopharyngiomas.³⁰

Conclusion

Patients with pituitary adenomas who undergo transphenoidal surgery require complex, multidisciplinary

peri-operative care to avoid complications. Careful optimization of management and follow-up strategies may have a significant impact on the quality of life and long-term survival of the patients.

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