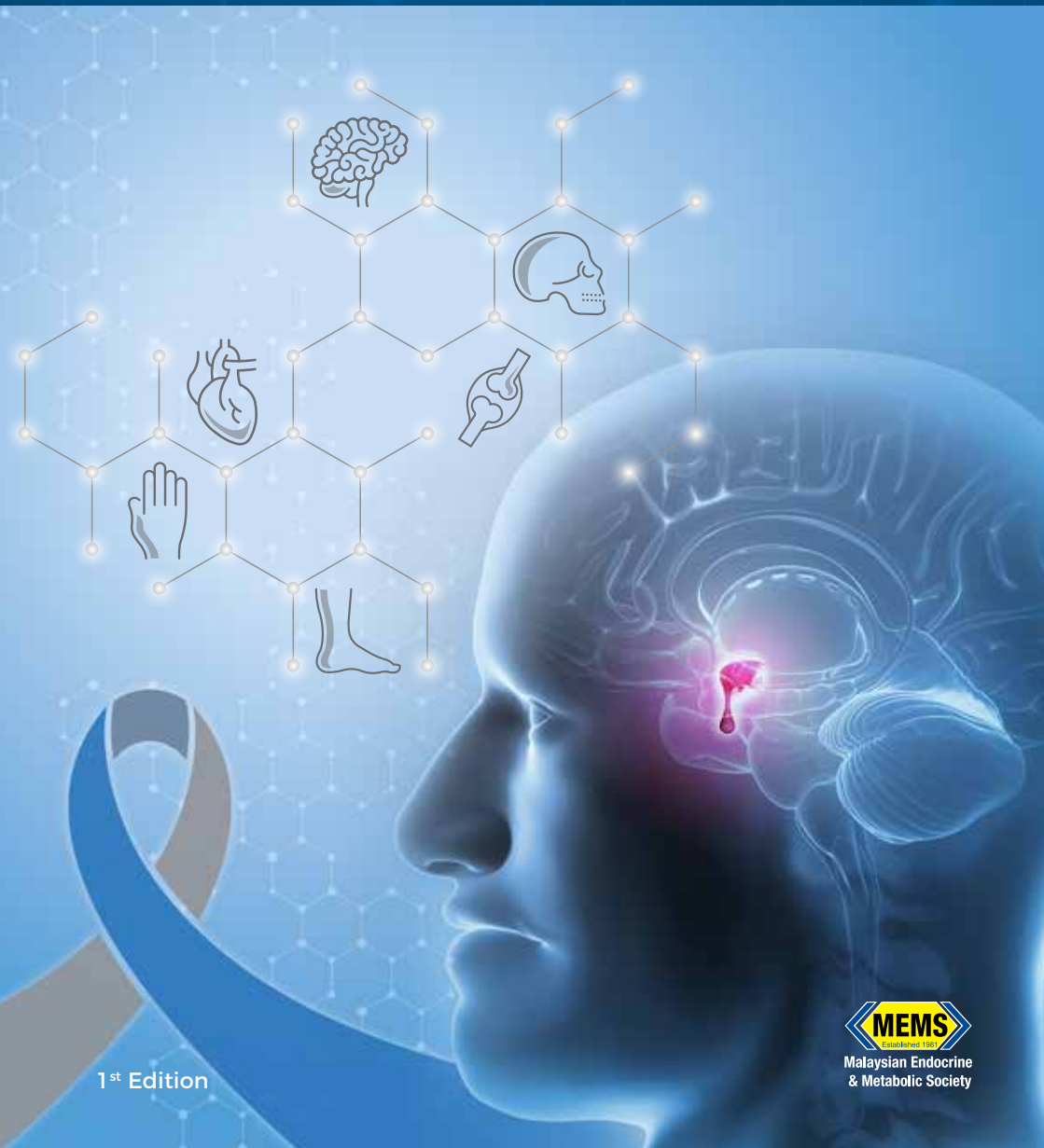
CONSENSUS STATEMENT FOR THE DIAGNOSIS AND MANAGEMENT OF ACROMEGALY



1st Edition

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TERMS OF REFERENCE

Target audience
The 1st edition Consensus Statement for the Diagnosis and Management of Acromegaly is aimed at healthcare providers involved in providing clinical management to patients suspected of or diagnosed with acromegaly.

Statement of intent
The recommendations within this document are based on the best available and current evidence, knowledge and clinical experience at the time of its development. These are not rigid, but serve as guides on the best approaches in acromegaly management. They have been tailored to the Malaysian setting and the final management decisions must be made via a multidisciplinary approach and individualised to the needs of each patient based on the available resources.

Format
The contents of this consensus are based on the latest available evidence in the diagnosis and management of acromegaly, best practice recommendations from internationally recognised bodies and the best practices performed within the country.

Period of validity
The recommendations within this consensus statement were developed in 2019 and will be reviewed within 5 years (2024).

Disclosure
None of the writing committee members declare any conflict of interest.

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The contents of this consensus statement do not guarantee the best outcomes in every patient and therefore, the responsibility in managing an acromegaly patients lies with the individual healthcare provider depending on the patient's clinical manifestations and the diagnostic and therapeutic options available.

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CHAPTER 1
INTRODUCTION

Acromegaly is an uncommon clinical syndrome resulting from excessive growth hormone (GH) production. In most cases, it arises from a GH secreting pituitary adenoma with resultant increased production of insulin-like growth factor-1 (IGF-1) from the liver. Both hormones exert characteristic changes and growth effects on major organ, skeletal and soft tissues. The resultant insulin resistant state leads to predisposition of developing glucose intolerance, metabolic dysfunction and increased cardiovascular risk with associated co-morbidities such as hypertension, obstructive sleep apnoea (OSA) and arthritis. The pituitary tumour, typically a macroadenoma, can contribute to local mass effect with complications such as visual disturbance and hypopituitarism.

There needs to be better awareness of the condition among primary care doctors and other specialties, and a need for improved screening to identify patients and earlier referral to endocrinologists for confirmation of diagnosis and treatment initiation.

Main aims of treatment in acromegaly are to reduce and restore GH and IGF-1 levels to normal range, as this is associated with control of symptoms, prevention and control of complications, and reduction in morbidity and mortality. Treatment choices include surgical, medical and radiation therapy (RT) needing long-term multidisciplinary monitoring.

A multidisciplinary team should assess every newly diagnosed acromegaly patient to ensure individualised plan of treatment. Comprehensive care and follow-up should be accessible via a dedicated pituitary clinic led by an experienced endocrinologist, with access to neuroimaging and endocrine laboratory facilities that provide appropriate assays for prompt measurements of GH and IGF-1.

Currently there are no available guidelines addressing the diagnosis and management of patients with acromegaly in Malaysia. This consensus has been developed to standardise the management of this uncommon disease in Malaysia. Prompt and optimal resource allocation and utilisation for the management of acromegaly will enable patients to achieve a good quality of life with reduction of chronic complications and co-morbidities. Ultimately, this strategy will contribute to reduction in disease-related burden on the Malaysian healthcare system and contribute to true cost savings in the long-term.

METHODOLOGY

This consensus statement is based on latest best practice recommendations of the Endocrine Society[1] and American Association of Clinical Endocrinologists (AACE)[2] guidelines, and a comprehensive review of current medical literature. The recommendations were then developed with consensus building through face-to-face meetings by a multidisciplinary group of Malaysian specialists involved in the care of acromegaly patients consisting of endocrinologists, neurosurgeons, radiologists, radiation oncologists and laboratory specialists. The local recommendations were then carefully formulated taking into consideration the Malaysian healthcare system and the local availability and accessibility of diagnostic procedures and management options for patients with this disease. This was then circulated to a group of external reviewers in the same specialties and practicing within Malaysia for further review and feedback, which were taken into consideration resulting in these final recommendations.

CHAPTER 2

EPIDEMIOLOGY

Acromegaly is a rare disease with significant risk of mortality.

Overview of acromegaly epidemiology	
Prevalence	(Western countries) 70-80 cpmp/year[3-6] (Some Asian countries) 28 cpmp/year[7]
Incidence	(Western countries) 3-11 cpmp/year[3-6] (Some Asian countries) 4 cpmp/year[7]
Gender distribution	Male and female equally affected[3,4,7]
Mean age of diagnosis	mid-40-50s[3,7-9]
Confirmation of diagnosis	Average of 4-7 years delay from onset of GH hypersecretion[3,4,10]
Cause	> 95% are due to GH secreting pituitary tumours arising from somatotroph cells[1] Rare causes are non-pituitary neuroendocrine tumours that cause ectopic secretion of growth hormone releasing hormone (GHRH) which may be bronchial, pancreatic, gastrointestinal, thymic and tumours associated with Multiple endocrine neoplasia type 1 (MEN1)
Types of pituitary tumours	70% - macroadenomas (≥ 1 cm in diameter)[3] 30% - microadenomas (< 1 cm in diameter)[3]
Treatment outcomes	Microadenomas - 80-90% chance of surgical cure in the hands of high volume pituitary surgeons[3]
	Macroadenomas – 40-50% chance of surgical cure - Achieving disease control is challenging even with combination treatment of surgery, RT and medical therapy - Treatment options are costly - Requires a sensible and schematic selection of patients for specific modalities of treatment
Mortality risk	Individuals with uncontrolled disease have at least a 2-fold increase in mortality risk compared to the general population[1,11-13] The most common cause of mortality is from cardiorespiratory diseases

There are at present very limited Malaysian epidemiological data available for acromegaly.

- From unpublished observational data of the Malaysian Acromegaly Registry, acromegaly appears to be seriously under-recognised and under-diagnosed in the country with fewer than 150 patients being managed at established endocrine centres.
- However, from the cases series collected, the ratio of male to female is similar with other countries.

CLINICAL FEATURES

Common clinical features in acromegaly	
Most common presentation	Headache[14] Enlarged facial features[10,14-16] - enlargement and protrusion of the lower jaw (prognathism) + dental malocclusion, overbite, interdental separation Acral enlargement[10,14-16] - increasing ring and shoe size
Common co-morbidities	Diabetes mellitus Hypertension Cardiomyopathy Obstructive sleep apnoea (OSA) Multinodular goitre
Other features[16,17]	Visual field defects typically bitemporal hemianopia Hyperprolactinemia Hypopituitarism (hypogonadism, hypothyroidism and hypocortisolism) Colonic polyps Visceromegaly Carpal tunnel syndrome (CTS) Large joint pain Oily perspiration Multiple skin tags Acanthosis nigricans

CHAPTER 3
DIAGNOSIS

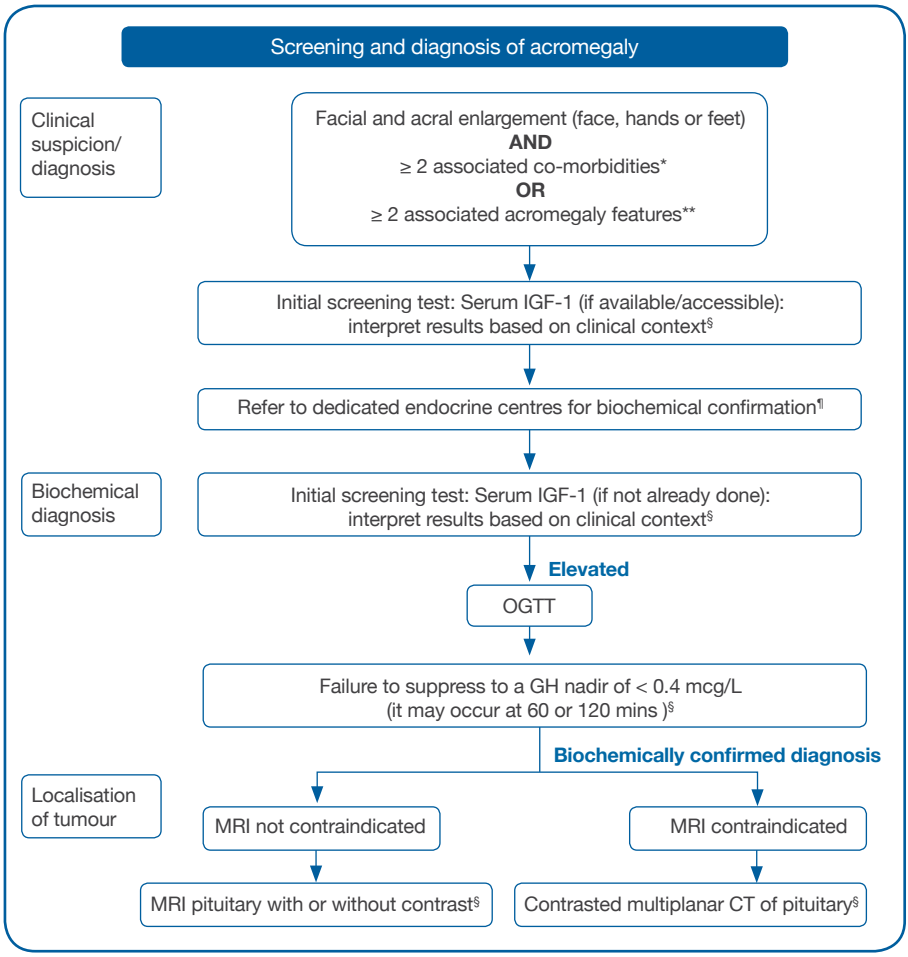

Figure 1: Screening and diagnosis of acromegaly algorithm.

*Diabetes mellitus, hypertension and heart disease of uncertain aetiology; **Complaints of headache, obstructive sleep apnoea, colonic polyps, large joint pains, carpal tunnel syndrome, sweaty/oily hands, multiple skin tags; § Please see text below for more information; ¶ Refer to centres with a multidisciplinary team dedicated to management of acromegaly that includes endocrinologists, neurosurgeon and radiologist, and if available a radiation oncologist.

IGF-1: insulin like growth factor-1; OGTT: oral glucose tolerance test; MRI: magnetic resonance imaging; CT: computed tomography scan.

CLINICAL DIAGNOSIS

Recommendation:

1. If a clinician encounters a patient with enlargement of the facial features, hands or feet with two or more co-morbidities or features associated with acromegaly they should refer him/her to an endocrinologist, preferably in a dedicated endocrine centre.

These include the presence or complaints of:

- headache,
- diabetes mellitus,
- hypertension,
- heart disease of uncertain aetiology,
- OSA,
- colonic polyps,
- large joint pains,
- CTS,
- sweaty/oily hands; or
- multiple skin tags.

Once clinical diagnosis or clinical suspicion of acromegaly is made, all patients should be referred to dedicated endocrine centres for biochemical confirmation of acromegaly.

BIOCHEMICAL DIAGNOSIS

Recommendations:

1. When a clinical suspicion of acromegaly is established, serum IGF-1 should be measured as an initial screening test as it is the most sensitive and specific test for diagnosis.
2. An oral glucose tolerance test (OGTT) in patients with elevated IGF-1 that fails to suppress GH confirms diagnosis of acromegaly.
3. When a highly sensitive GH assay is used in the context of an elevated serum IGF-1, a nadir GH of > 0.4 mcg/L is consistent with a diagnosis of acromegaly.

IGF-1 levels

- The levels should be interpreted using assay-specific age and gender matched reference ranges developed by the assay manufacturer.
- However, as there are various conditions that may elevate (e.g. puberty, pregnancy and hyperthyroidism) or lower (e.g. malnutrition, liver failure, renal failure, oral oestrogen use, untreated hypothyroidism and uncontrolled diabetes) serum IGF-1 levels, clinical context must be considered when interpreting the results.[18,19]

OGTT

- Simultaneous OGGT done without IGF-1 levels is justified in patients with a very high index of clinical suspicion to minimise diagnostic delay.
- The nadir GH level is seen between 60-120 minutes following an oral glucose load, thus GH measurements are recommended to be taken at 0, 60 and 120 minutes during the OGTT[2,20]
- Failure to suppress GH levels to < 1.0 mcg/L during OGTT (at 120 minutes) is considered diagnostic of acromegaly.[1]

IGF-1 and GH discordance

- Refers to elevated IGF-1 with nadir GH < 1mcg/L during OGTT.
- With improvement in the sensitivity of modern GH assays, it has been established that in normal individuals, the nadir GH is < 0.3 mcg/L.[21]
- Depending on the sensitivity and accuracy of the GH assay used, some authorities advocate using a cut-off of 0.4 mcg/L during an OGTT to diagnose acromegaly.[2]
- Discussion with a laboratory biochemist is required to establish sensitivity of GH assay in use.

Random GH or mean GH levels is not recommended to make an initial diagnosis of acromegaly due to poor specificity.[1]

IMAGING

Recommendations:

1. Magnetic resonance imaging (MRI) pituitary protocol with and without contrast is the neuroimaging investigation of choice in patients with acromegaly confirmed by biochemical diagnosis.
2. All patients should have their renal function tested as a routine.

- MRI pituitary is the preferred diagnostic imaging modality to evaluate sellar and parasellar tumours.
- Offers high contrast and multiplanar thin cuts[22] enabling the evaluation of small soft tissue changes.
- Protocols should include pituitary sequences, 3 mm thick slices with Coronal T1WI /T2WI /T1 post-gadolinium and Sagittal T1WI /T1 post-gadolinium with or without a dynamic study.
- Optional added brain sequences include, T2WI axial and T1 axial post-contrast sequences.
- A dynamic MRI pituitary may be useful particularly when functioning microadenomas are suspected as, it obtains images within seconds after administration of gadolinium.[23]

Computed tomography

- Computed tomography scan (CT) of the pituitary is only suggested in patients where MRI is contraindicated, as anatomical details are less defined.[2]
- Less commonly done in Malaysia.
- If necessary, CT of pituitary should be done with use of contrast and must include multiplanar reformats.

CHAPTER 4

MANAGEMENT

Management

The management of acromegaly involves multimodal therapy.[1,2,24,25] Decisions should ideally be made via multidisciplinary team (MDT) meetings involving endocrinology, neurosurgery, neuroradiology, oncology, ophthalmology and pathology specialities. Hence, the management of acromegaly patients in Malaysia should be centred in major public, university and private hospitals with established expertise in these disciplines.

Goals of management

The main goals in acromegaly treatment[1,2] are:

- tumour shrinkage
- reduction of GH (< 1 mcg/L)
- normalisation of IGF-1[26]
- resolution of clinical symptoms
- improvement in co-morbidities
- reduction in long-term mortality

Types of management

- **Surgery**, is the recommended first line treatment[1,2] of acromegaly in Malaysia.
- **Medical therapy** with somatostatin receptor ligands (SRL) and dopamine agonists (DA) such as cabergoline are also available.
- Locally, despite advancements in surgical techniques and medical therapy, **radiotherapy**[27] still has an important role as salvage therapy. Indications for RT include:
  - patients unfit for or who refuse surgery
  - residual or recurrent tumours not amenable to repeat surgery
  - failed medical therapy.[27,28]

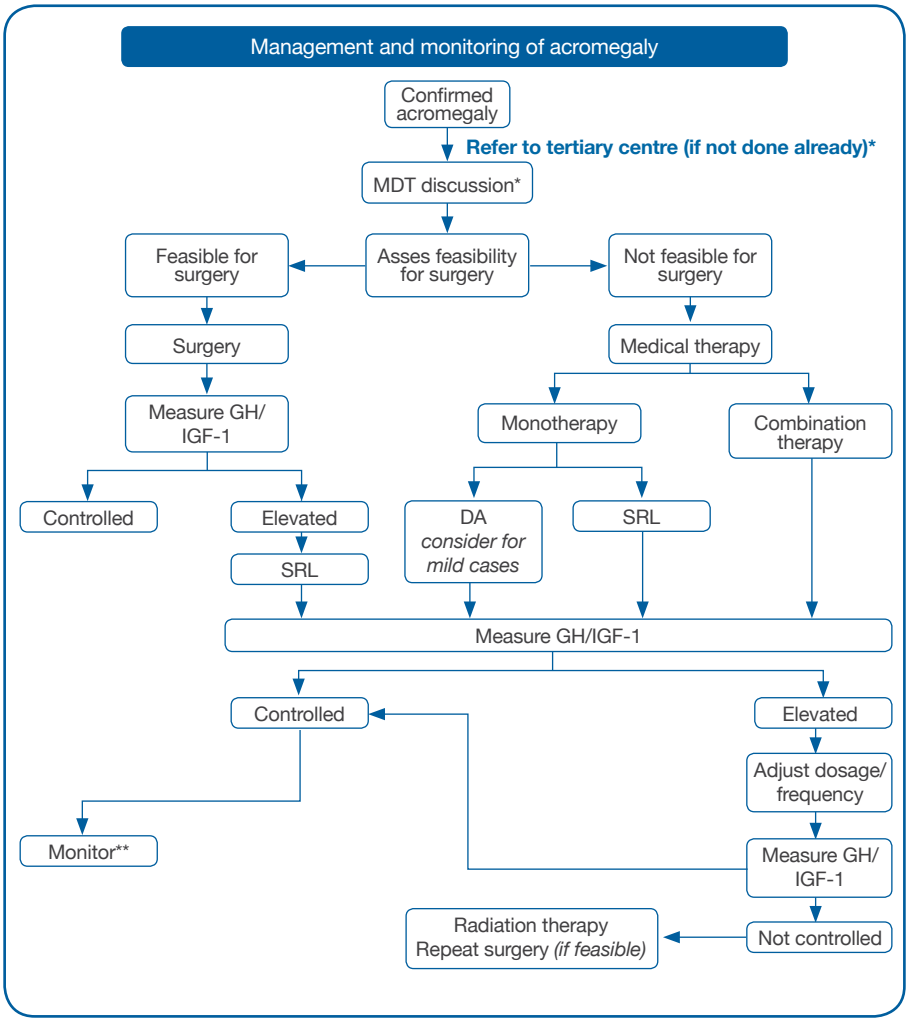

Figure 2: Management and monitoring of acromegaly patients.

*Refer to centres with a multidisciplinary team dedicated to management of acromegaly that includes endocrinologists, neurosurgeon and radiologist, and if available a radiation oncologist; ** Refer to section on monitoring for details.

MDT: multi-disciplinary team; DA: dopamine agonist; SRL: somatostatin receptor ligands; IGF-1: insulin like growth factor-1; GH: growth hormone

SURGERY

Recommendations:

1. In most patients diagnosed with acromegaly, surgery is the recommended first line treatment followed by medical therapy and RT, should surgery not be curative.[1,2,29]
2. Well-coordinated multidisciplinary team approach in the surgical management of acromegaly can offer optimal treatment with better outcomes and lower morbidity.[1]
3. Trans-sphenoidal surgery (TSS) is the treatment of choice.
4. Recommended imaging modality of choice for pre-operative evaluation is MRI.
5. Selective adenomectomy via trans-sphenoidal-trans-nasal route is the preferred technique.
6. Image Guided Surgery protocol is strongly recommended when normal anatomical landmarks are altered or destroyed.
7. Vascularised mucoperiosteum-mucoperichondrium nasoseptal flap is the preferred choice when reconstruction of the sellar defect is required.

Goals of surgery

- To achieve cure.
- To avoid life long post-operative hormonal replacement therapy.
- Aggressive and complete removal of GH secreting tissue is therefore advocated whenever possible, whilst attempting to identify and preserve the remaining normal pituitary tissue.[2]

Pre-operative evaluation and surgical planning

Pre-operative evaluation should consist of imaging and management of co-morbidities.

Imaging modalities	
MRI	**Pre-operative evaluation** • Recommended imaging modality of choice. • Use high resolution MRI with pituitary protocol to: ➢ help localise the tumour ➢ visualise fine anatomic details surrounding the tumour and its neighbouring sites ➢ identify presence of haemorrhage or tumour necrosis **Planning for surgery** • MRI for Image Guided Surgery protocol is recommended when planning for: ➢ removal of macroadenoma with cavernous sinus invasion ➢ destruction of sellar floor ➢ poor pneumotisation of sphenoid sinus ➢ repeated surgery ➢ micro adenoma with normal size sellar turcica
Dynamic contrast enhanced multisection CT of pituitary	**Pre-operative evaluation** • When MRI is contraindicated/unavailable.
Computer assisted imaging navigation	**Pre-operative evaluation and planning for surgery** • Provides 3-dimensional (3-D) mapping of tumour margins in relation to surrounding tissues. • Serves as a guide to safe resection and improving outcomes.
High resolution CT of pituitary	**Pre-operative evaluation and planning for surgery** • May be required in presence of significant bony enlargements within nasal cavity and skull base. • Serves to determine the necessity of an adjunct endonasal surgical procedure.

Surgical procedures

The ability to rapidly normalise GH and IGF-1 levels, compared to medical and RT, makes trans-sphenoidal surgery (TSS) the treatment of choice.[29] For large and invasive tumours, debulking surgery is suggested to relieve compressive symptoms and to enhance response to medical therapy.[1,2] Therefore, it is also advocated in patients where surgical cure is not feasible due to tumour location or invasiveness.[29] Repeat surgery is recommended when there is elevated IGF-1 in the presence of an accessible residual or recurrent tumour.

Surgical techniques

Surgical techniques and approaches	
Selective adenomectomy via trans-sphenoidal-trans-nasal route	• Preferred surgical technique. • Emphasises targeted and minimally invasive approach. • Done with either an operating endoscope or microscope for visualisation and microsurgical techniques.[1,2]
Partial hypophysectomy	• Considered where: ➢ tumours are not visualised well on MRI ➢ tumours are unidentifiable during surgery despite biochemical confirmation • In failed remission, may require a more aggressive approach during repeat surgery.
Conventional microscopic sublabial trans septal approach	• Alternative approach
Endoscopic assisted trans nasal microsurgery	• Alternative approach
Transcranial surgery	• For large tumours with significant extension to suprasellar, intraventricular, lateral, parasellar or fronto-temporal regions. • Tumours involving critical neuromuscular structures. • Approach used should be tailored to the tumour size and extension.

In large and invasive tumours, multiple approaches may be required.

Reconstruction of the sellar defect after tumour removal with vascularised mucoperiosteum-mucoperichondrium nasoseptal flap is the preferred choice for large defects or in the presence of an intraoperative cerebrospinal fluid (CSF) leak.

Additionally, Image Guided Surgery protocol is strongly recommended when normal anatomical landmarks of the nasal cavity and endonasal skull base are altered or destroyed by a large tumour or previous surgery.

MEDICAL THERAPY

Recommendations:

1. SRL is recommended as secondary (adjuvant) therapy in the presence of residual disease without mass effects after primary surgery.[1,2,25]
2. SRL is used as primary therapy when surgical cure is unlikely or patients are unfit or refuse surgery.[1,2]
3. DA may be used when there are modest elevations in IGF-1.
4. Combination treatment with SRL and DA is recommended in patients who have only partial control with SRL monotherapy.
5. Second generation SRL (pasireotide LAR) should be considered when octreotide LAR or lanreotide alone or in combination with cabergoline fail to control IGF-1.

SRL is the mainstay medical therapy for acromegaly. As long-term indefinite use of medical therapy with SRL is heavily limited by its cost in the Malaysian setting, most patients with residual disease are offered other definitive treatment options such as repeat surgery and/or RT.

Somatostatin receptor ligands

SRL therapy	Indications for SRL
Primary therapy	• Macroadenomas with extrasellar extension particularly into the cavernous sinus, without mass effect or chiasmal compression where surgical cure is unlikely.[1,2] • In patients who are poor surgical candidates (e.g. age and co-morbidity restrictions).[1,2] • Those who refuse surgery.
Secondary therapy	• Presence of residual disease without mass effects after primary surgery.[1,2,25] • Commonly used as bridging therapy while awaiting second surgery or RT to take effect.
Pre-operative (neo-adjuvant) treatment	• Limited use to those with severe pharyngeal thickness, sleep apnoea or heart failure to improve surgical outcomes.[1,30]

- The two commonly used SRL in Malaysia are the intramuscular (IM) **octreotide long-acting release** (LAR) and subcutaneous (SC) **lanreotide** depot formulations that are administered four weekly.
- Most physicians in Malaysia do not use a test dose of short acting (SA) octreotide prior to commencing the long-acting formulation.

	IM octreotide LAR	SC lanreotide
Dose strengths available in Malaysia	• 20 mg and 30 mg doses.	• 120 mg dose.
Efficacy	• Both are similar[1,2,31] with an expected GH control to safe levels (< 2.5 mcg/L) and/or IGF-1 normalisation in 34-55% of patients.[32-36] • With SRL, a clinically relevant reduction in tumour volume (> 20%) is seen in 53-63%[37,38] of patients.	
Method of administration	• Requires reconstitution and administration by a healthcare professional.	• Pre-filled ready to use pen allowing partner or self-injection.[39]
Recommended starting dose	20-30 mg/4 weekly	120 mg/4 weekly
Dosing schedule	• 4-weekly. • With improvement in clinical and biochemical parameters, physicians may extend the dosing intervals up to:[40,41] ➢ 8-12 weekly for octreotide LAR ➢ 6-8 weekly for SC lanreotide • If standard dosing (lanreotide 120 mg and octreotide 30 mg) does not achieve control, the frequency may be increased to 3 weekly.[42,43]	
Adverse events	• Mainly abdominal cramps and diarrhoea, which are temporary. • Formation of gall bladder sludge and stones may occur. • Abdominal ultrasound is required in patients who present with symptoms of gall bladder disease.[1]	

Pasireotide LAR, second generation SRL can be used in selected cases when octreotide LAR or lanreotide alone or in combination with cabergoline fail to control IGF-1, as data show better efficacy with this agent.[35,44,45]

However, its use is limited by very high cost and to patients without poorly controlled glucose, as there is a high rate of worsening hyperglcaemia seen up to 70% of treated patients.[35]

Dopamine agonists

- Mainly used for mild residual disease (IGF-1 < 2 times upper limit of normal; ULN)[47] or when cost limits the use of SRL.
- Has the added benefit of being orally administered.
- Used irrespective of prolactin co-secretion.
- **Though a less effective form of treatment, dopamine agonists may be used in Malaysia as bridging therapy while awaiting effects of RT or second surgery**.

Cabergoline is the only DA that has been widely studied and recommended for use in acromegaly.[47,48]

- 30% of patients reached normalised IGF-1 when it was used as a single agent.
- The recommended dose of cabergoline is between 1.5-3.5 mg/week.
- Patients should be warned of its side effects such as nausea, hypotension and headaches prior to initiating treatment.
- All patients on cabergoline should have an annual clinical cardiovascular examination to detect valvulopathy.[49]
- Echocardiogram (ECHO) should be reserved for patients:
  - with audible murmur
  - on cabergoline ≥ 3 mg/week for more than five years or equivalent cumulative dose[46]
  - on maintenance treatment with cabergoline after the age of 50 years.[49]

Combination treatment with SRL and DA is recommended in patients who have only partial control with SRL monotherapy[50,51] with 42-44% of patients, uncontrolled on single therapy, reaching normal IGF-1 levels with combination therapy.[2,50]

Generally considered a weak agent, **selective oestrogen receptor modulators (SERMs)** or oral oestrogen[2,52] may be used in combination with SRL and DA.

- This may be an option for patients who cannot afford the use of SRL alone in mild disease.
- However, this combination is not practiced commonly in Malaysia and experience is therefore limited.

GH receptor antagonist

Pegvisomant, the GH receptor antagonist is the most effective medical therapy for acromegaly.[46] However, it is currently unavailable in Malaysia.

RADIOTHERAPY

Recommendations:

1. Fractionated RT should be delivered using 3-D conformal radiation technique with CT of pituitary image acquisition.
2. Dose of fractionated RT with 1.8-2 Gray (Gy) per day (up to a total dose of 54 Gy) is recommended.
3. IMRT and FSRT are preferred, as it significantly reduces dose of radiation to normal tissues and incidence of long-term toxicities.
4. SRS is preferred if available. There must be a minimum distance of tumour to optic chiasma of 3 mm and a margin dose of 18-25 Gy is recommended.
5. Interruption of somatostatin analogue during RT should not be routinely adopted in our setting.

Indications for intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT) or streotactic radiosurgery (SRS) are normally reserved for residual or recurrent tumour cases where risk of surgery is high or when patients refuse surgery.

RT services including FSRT are available in 4 out of 5 Ministry of Health, Malaysia centres. IMRT is available in all centres whilst SRS is offered in Kuala Lumpur General Hospital and the National Cancer Institute.

Therefore, fractionated RT with 1.8-2 Gray (Gy) per day (up to a total dose of 54 Gy) is the recommended standard approach toward irradiating secreting pituitary adenomas.

- This results in tumour growth control in 80-90% and normalisation of GH/IGF-1 in 50-60% of patients at 10 years.[53]
- Rapid decrease in GH occurs in the first two years followed by progressive, slow decrease over 10-20 years.[54]
- Median onset of biochemical remission is between 7-10 years.[55]
- Hypopituitarism occurs in up to 60% of treated patients and its onset follows a similar time course as the development of remission.
- Long term side effects that should be followed up:[55]
  - optic neuropathy (1-5%)
  - brain necrosis (< 1%)
  - cerebrovascular accident
  - second intracranial neoplasms (1-2%)

Fractionated RT should be delivered using 3-D conformal radiation technique with CT of pituitary image acquisition[53] and is consistent with local practice. IMRT and FSRT are preferred, as it significantly reduces dose of radiation to normal tissues and incidence of long-term toxicities.[53]

SRS is preferred[56] if appropriate equipment such as linear accelerator, gamma knife or Cyberknife, and trained personnel are available.

- Minimum distance of tumour to optic chiasm of 3 mm needs to be fulfilled for this approach to be possible.[53]
- A margin dose of 18-25 Gy is recommended.
- Though long-term tumour control rate of 80-90%, similar to fractionated RT, is achievable, its strength lies in earlier normalisation of GH/IGF-1 as early as 1.4 years (median 4.5 years).[55]
- Risk of long-term side effects are further reduced, even though hypopituitarism still remains common reaching up to 50% in some case series.[28,53]

As data is conflicting in different case series,[54,55] interruption of somatostatin analogue during RT should not be routinely adopted in our setting. Patients who have received RT should be monitored with GH/IGF-1 and hormonal profiles annually.[1]

CHAPTER 5

MONITORING

Recommendations:

1. IGF-1 and random GH levels are recommended at 12 weeks post-surgery. If discordance present, repeat in 3-4 months.
2. First MRI pituitary should be 3-4 months post-surgery.
3. In presence of pre-operative visual field defects, repeat testing should be done regularly post-surgery.
4. IGF-1 and random GH levels monitoring are recommended for patients on SRL and/or DA. Monitor levels 4-6 weeks after any dose change.
5. IGF-1 and GH levels as well as pituitary function should be monitored annually in patients undergoing RT.
6. Regular assessment of co-morbidities and complications must be done.

GH and IGF-1 levels should be monitored to assess treatment efficacy and to detect persistent or recurrent disease.

Post-surgical	• Include both biochemical and imaging studies. **Biochemical testing:** • Immediate post-operative GH measurement is NOT recommended in local context. • IGF-1 level and random GH measurement are recommended at 12 weeks post surgery.[1] • GH value of < 1 mcg/L at 12 weeks: ➢ and a normal IGF-1 value (after age-dependent normalisation) by 3-6 months are consistent with surgical remission[2] ➢ indicates "control" and normalisation of mortality risk[1,57] • If GH is > 1 mcg/L, we suggest to measure nadir GH levels after an OGTT.[1] • Following surgical cure: ➢ an annual IGF-1 level measurement ➢ add OGTT if there is any suspicion of recurrence clinical or based on IGF-1 levels[2,57] • Discordance between GH and IGF-1 levels is seen in about 35% of patients with active acromegaly.[58] ➢ Repeat suggested 3-4 months after a discrepant result.[59] ➢ There is no specific guideline on the management of patients with discordant GH and IGF-1 levels. **Imaging studies** • First post-surgical MRI pituitary is recommended at least 3-4 months after the surgery.[2,60-62] • Subsequently based on disease activity.[2]

Post-surgical	**Visual field testing** In patients with pre-operative visual field defects, visual field testing should be done regularly post-surgery.[1]
Patients receiving medical therapy	**Biochemical testing** • For patients on SRL or DA it is recommended to monitor both GH and IGF-1 levels to assess response to treatment. • Disease monitoring should be done using IGF-1 and random GH levels.[63] • OGTT should NOT be used to monitor treatment response to SRL as it is unreliable. • Ideally monitored 4-6 weeks after any dose change.[2] **Adverse events** • Monitor adverse events associated with SRL such as gastrointestinal and metabolic disorders.
Patients receiving RT	Patients receiving RT are at risk of developing hypopituitarism, radiation-induced secondary tumours and radionecrosis. **Biochemical testing** • Annual GH and IGF-1 levels monitoring.[2,57] • Annual evaluation of pituitary function for hypopituitarism.
Co-morbidities	• Cardiovascular and cerebrovascular events are the main causes of death in patients with acromegaly. ➢ Cardiovascular risk factors should be appropriately treated and monitored. ➢ Patients with symptoms of OSA should have an overnight polysomnography done. ➢ ECHO and electrocardiography (ECG) should be performed in patients with suspected cardiac disease. ➢ Screening for hypertension and diabetes should be regularly performed. • Musculo-skeletal ➢ Signs and symptoms of CTS and arthropathy. ➢ Bone densitometry in patients with history of hypogonadism or fractures.[2] • Colon ➢ All patients should undergo colonoscopy once diagnosed with acromegaly[1,2] ➢ In patients with a colonic polyp at screening or with persistently elevated IGF-levels, repeat every 5 years. ➢ In those without any polyps at screening and/or with controlled disease, repeat every 10 years.[1] • Thyroid ➢ Ultrasound of the thyroid should be performed if there is palpable thyroid nodularity[1] in view of increased risk of thyroid cancer in acromegaly.[64]

ABBREVIATED INDEX

3-D	Three dimensional
AACE	American Association of Clinical Endocrinologists
cpmp	Cases per million population
CSF	Cerebrospinal fluid
CT	Computed tomography scan
CTS	Carpal tunnel syndrome
DA	Dopamine agonists
e.g.	For example
ECHO	Echocardiogram
FSRT	Fractionated stereotactic radiotherapy
GH	Growth hormone
GHRH	Growth hormone releasing hormone
Gy	Gray
IGF-1	Insulin-like growth factor-1
IMRT	Intensity modulated radiotherapy
LAR	Long-acting release
mcg	Microgram
MDT	Multidisciplinary team
MEN-1	Multiple endocrine neoplasia type 1
mg	Milligram
mins	Minutes
mm	Millimeter
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
OSA	Obstructive sleep apnoea
RT	Radiation therapy
SA	Short acting
SC	Subcutaneous
SERMs	Selective oestrogen receptor modulators
SRL	Somatostatin receptor ligands
SRS	Streotactic radiosurgery
TSS	Trans-sphenoidal surgery
ULN	Upper limit of normal

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