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SPECIAL ARTICLE

Executive summary of the expert consensus document from the Spanish Society of Neurosurgery and the Spanish Society of Endocrinology and Nutrition: Clinical recommendations on the perioperative management of pituitary tumors*

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Abstract Pituitary tumors (PT) account for 15% of intracranial tumors affect 10.7%–14.4% of the population although the incidence of clinically relevant PT is 5.1 cases/100,000 inhabitants. Surgical treatment is indicated in PTs with hormone hypersecretion (except for prolactin-producing PTs) and those with local compressive or global neurological symptoms. Multidisciplinary care, is essential for patients with PTs, preferably delivered in a center of excellence and based on a well-defined care protocol. In order to facilitate and standardize the clinical procedures for this type of tumor, this document gathers the positioning of the

* The full version of the document can be consulted online at: https://www.seen.es/portal/areas-knowledge/neuroendocrinologia/documentos/consensos-guias/recomendaciones-manejo-perioperaper-tumores-hipofisarios

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Non-functioning pituitary tumor;
Diabetes insipidus;
Hyponatremia;
Vasopressin deficiency;
SIADH

Neuroendocrinology Knowledge Area of the Spanish Society of Endocrinology and Nutrition (SEEN) and the Spanish Society of Neurosurgery (SENEC) on the management of patients with PTs and their preoperative, surgical and postoperative follow-up.

PALABRAS CLAVE
Tumor hipofisario;
PITNET;
Cirugía transesfenoidal;
Acromegalia;
Enfermedad de Cushing;
Adenoma hipofisario no funcionante;
Diabetes insípida;
Hiponatremia;
Déficit de vasopresina;
SIADH

Resumen ejecutivo del documento de consenso de expertos de la Sociedad Española de Neurocirugía y de la Sociedad Española de Endocrinología y Nutrición sobre: recomendaciones clínicas en el manejo perioperatorio de los tumores hipofisarios

Resumen Los tumores hipofisarios (TH) suponen el 15% de los tumores intracraneales y afectan del 10,7 al 14,4% de la población, si bien la incidencia de TH clínicamente relevantes es de 5,1 casos/100.000 habitantes. El tratamiento quirúrgico está indicado en los TH que cursan con hipersecreción hormonal (a excepción de los TH productores de prolactina), así como en aquellos con clínica compresiva local o neurológica global. Los pacientes con TH requieren una atención multidisciplinar, idealmente en un centro de excelencia y basada en un protocolo asistencial bien definido. Con el objetivo de facilitar y estandarizar la práctica clínica ante este tipo de tumores, el presente documento recoge el posicionamiento del Área de Conocimiento de Neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición (SEEN) y la Sociedad Española de Neurocirugía (SENEC) sobre el manejo y el seguimiento prequirúrgico, quirúrgico y posquirúrgico del paciente con un TH.

Introduction

Pituitary tumours (PT) account for 15% of all intracranial tumours. They are detected incidentally in 10.7%–14.4% of the population although the incidence of clinically relevant PT is 5.1 per 100,000 population/year, and the prevalence is higher than 100 cases per 100,000.[1,2] They are usually benign indolent adenomas,[3] but they can occasionally become aggressive and cause significant morbidity.[4] When there is local compression or hormone hypersecretion, surgery is usually the treatment of choice, except for prolactinomas, where surgery is reserved for cases with resistance or intolerance to medical treatment and/or acute visual impairment.[1,5,6]

Ideally, PT patients should be looked after by an expert multidisciplinary team (including at least endocrinology, neurosurgery, neuroradiology and ophthalmology), which, after assessing each case, will decide on and plan the necessary care, including the indication for surgery.[7]

No European consensus document[8] has been published to date on the perioperative management of patients with PT. The Neuroendocrinology Area of the Sociedad Española de Endocrinología y Nutrición (SEEN) [Spanish Society of Endocrinology and Nutrition] has brought together a group of endocrinologists and neurosurgeons with expertise in this disease to draw up a multidisciplinary consensus document on the peri-surgical management of patients with PT.

Indications for surgery for pituitary tumours

Pituitary surgery is indicated in tumours of the sellar region with hormone hypersecretion (except prolactin), with local compressive symptoms (chiasm, optic nerves, oculomotor nerves or hypopituitarism), or with overall neurological symptoms (for example, hydrocephalus and intracranial hypertension).

In the case of prolactin-secreting PT, surgical intervention with curative intent has been proposed as first-line treatment in women with macroprolactinomas with wish to become pregnant in the short term.[9]

Surgical indications for PT and other lesions of the sellar and parasellar regions[10,11] are summarised in Table 1.

Pre-surgical management of pituitary tumours

Pre-surgical medical treatment of hormone hypersecretion

Acromegaly

Pre-surgical treatment with first-generation somatostatin analogues (SSA-1 G) for three to six months is indicated in patients with severe pharyngeal thickening, sleep apnoea or high output heart failure.[12] In clinical practice, it is often indicated when there is a lengthy waiting period for surgery, as well as in patients with invasive macroadenomas with

Table 1 General indications for pituitary surgery in PT and other sellar lesions.

Indications for primary surgery in PT
- Functioning PT other than prolactinomas: acromegaly[12]; TSHoma[52]; Cushing's disease[53]; gonadotropinomas.
- Prolactinomas resistant to medical treatment or cases with intolerance to medical treatment.[9,54] Prolactinomas with significant cystic component and associated visual compression or with significant acute or rapidly progressive visual compromise.
- Symptomatic non-functioning PT > 1 cm: with compressive symptoms (visual loss, ophthalmoparesis, neurological deficits, obstructive hydrocephalus, headaches [refractory, not attributable to other causes]), close to or compressing the chiasm or optic nerves and/or with signs of hypopituitarism.[35]
- Asymptomatic non-functioning PT > 2 cm or with progressive growth on imaging tests.[35,55]
- PT associated with pituitary apoplexy presenting with a severely altered level of consciousness and/or decreased visual acuity and/or severe visual field defects which are acute, persistent or progressively deteriorating.[56]

Indications for re-intervention in PT
- As a matter of urgency
  - Acute epistaxis unresponsive to conservative treatment.
  - Postoperative tension pneumocephalus
  - Intracranial bleeding with mass effect.
- Planned
  - Previous subtotal resection with clinically or radiologically significant mass effect on the visual pathway.
  - Persistent hormone overproduction after failed pituitary surgery with resectable tumour on MRI or 11C-methionine PET.
  - Progressive growth of surgically accessible or resectable residual tumour, especially after failure of other second-line options (drugs or radiotherapy).
  - PT reduction to facilitate effective radiotherapy/radiosurgery.

Indications for surgery in other lesions of the selar/parasellar region
- Craniopharyngioma.[10]
- Suspected pituitary metastasis associated with compressive symptoms.[11]
- Any other sellar lesion associated with compressive symptoms, near or compressing the chiasm or optic nerves and/or with signs of hypopituitarism.

MRI: magnetic resonance imaging; PET: positron emission tomography; PT: pituitary tumour; TSHoma: thyrotropinoma.

little chance of surgical cure. Treatment guidelines are summarised in Table 2.

Cushing's disease

In Cushing's disease, pre-surgical control of hypercortisolism should be sought to minimise surgical morbidity and mortality.[7,13] Centrally-acting drugs which modulate ACTH secretion, adrenal steroidogenesis inhibitors and glucocorticoid (GC) receptor antagonists are available for this purpose (Table 2).

TSH-secreting pituitary tumours

Prior to intervention, treatment with SSA-1G, generally in combination with propranolol, is advisable to normalise thyroid function.[14,15] (Table 2).

Pre-surgical medical treatment of hormone deficiencies

Ideally, pituitary function should be assessed prior to surgery and any ACTH or TSH deficiency and ion imbalance should be corrected, as indicated in Table 3.

Perioperative glucocorticoid coverage

Perioperative coverage with GC is only recommended in the following scenarios: patients with confirmed adrenal insufficiency (AI); cases where the integrity of the adrenal axis could not be assessed; patients previously on long-term treatment with GC; and cases where the surgical procedure is expected to result in ACTH deficiency (total hypophysectomy or section of the pituitary stalk or surgery for Cushing's disease or pituitary apoplexy)[16] (Table 3).

Antithrombotic and antibiotic prophylaxis

Cushing's disease increases the incidence of venous thromboembolic events more than tenfold compared to patients with non-functioning PT undergoing surgery.[17,18] Therefore, treatment with low molecular weight heparins is recommended 2–14 days preoperatively and up to 2–6 weeks postoperatively[19] in higher risk patients: history of embolism; abnormal coagulation tests; severe hypercortisolism; oestrogen therapy; poor mobility; prolonged hospital stay; high postoperative cortisol concentrations; and high-dose GC replacement therapy in patients with AI.

Antibiotic prophylaxis significantly reduces the rate of postoperative infections[20] so intravenous administration of antibiotics is recommended in the anaesthetic induction for pituitary surgery.[21] In addition, in the case of the endonasal endoscopic approach,[22] antibiotic therapy is recommended for 24—48 h post-intervention.[23]

Surgical procedures

Goals of surgery

The goals of surgery in PT are: 1) tumour excision; 2) decompression of the visual pathway and pituitary gland tissue; and

Table 2 Preoperative medical treatment of hypersecretion and hormone deficiencies: indications and treatment guidelines.

Clinical condition	Indications	Treatment guidelines
Acromegaly	• Severe pharyngeal thickening and sleep apnoea, or high output heart failure.[12]	• *Octreotide LAR*: *im*, starting dose 20 mg/month. Maximum dose: 40 mg/month
	• If excessive delay in surgery	• *Lanreotide autogel*: *sc*, starting dose 90 mg/month. Maximum dose: 120 mg/month
	• Consider in invasive PT > 1 cm where incomplete tumour resection is expected	*Consider higher starting doses in somatotropinomas which are large or have very high levels of IGF1 and GH. Treatment should be maintained for 3–6 months prior to surgery.*
Cushing's disease	• Severe CD*: with life-threatening metabolic, psychiatric, infectious, cardiovascular or thromboembolic complications.[19]	• *Ketoconazole:* 200—1000 mg/day
	• If excessive delay in surgery.[19]	• *Metyrapone:* 500—6000 mg/day • Other less common therapies in the preoperative period: osilodrostat 4—14 mg/day; levoketoconazole 300—1,200 mg/day; cabergoline 0.5—7 mg/week; pasireotide 10–30 mg/month; mifepristone 300—1200 mg/day; etomidate in ICU setting.
TSH-secreting PT	• Cases of severe hyperthyroidism or delayed pituitary surgery.[14,15,52]	• *Octreotide LAR*: *im*, starting dose 20 mg/month. Maximum dose: 40 mg/month • *Lanreotide autogel*: sc, starting dose 90 mg/month. Maximum dose: 120 mg/month • *Propranolol:* 80—120 mg/day • *Exceptionally, antithyroid treatment may be necessary.* *Thiamazole* 20/30 mg/day or *propylthiouracil* 200—300 mg/day; or even thyroidectomy

CD: Cushing's disease; GH: growth hormone; IGF1: insulin-like growth factor-1; im: intramuscular; sc: subcutaneous; PT: pituitary tumour; TSH: thyroid-stimulating hormone; ICU: intensive care unit.
* If there is a need for rapid normalisation of cortisol, treatment with an adrenal steroidogenesis inhibitor is recommended; osilodrostat and metyrapone are the fastest acting and are available orally.[19]

3) remission of endocrine disease caused by hyperfunctioning tumours.

Surgical procedures

The endoscopic approach is currently the most widely used technique.[24] The transcranial approach is indicated when the PT has invaded the brain or is surrounding the vessels in the circle of Willis or the optic nerves.[25]

Selection of surgical approach and technique

Transsphenoidal approach

After proper positioning of the patient on the operating table, three surgical phases are performed: 1) Nasal phase: lateral dislocation of the middle turbinate to expose the sphenoethmoidal recess; 2) Sphenoidal phase: opening of the anterior sphenoid wall to expose the sella turcica and the parasellar neurovascular structures; and 3) Sellar phase: incision of the dura mater to begin tumour removal.

In microadenomas, it is recommended that the surrounding pseudocapsule be identified for complete excision. The tumour core is first emptied in *macroadenomas*, followed by extracapsular resection.[26] Finally, sellar reconstruction is mandatory to seal the cerebrospinal fluid compartment.

Transcranial approach

The option most commonly used is the frontotemporal (pterional) approach.

Complementary intraoperative techniques

Navigation

Use of a navigation system is recommended in cases where there are no identifiable intraoperative anatomical references: reinterventions; giant tumours engulfing the carotid artery and invading the spheroid sinus; in the presence of vascular abnormalities; and anatomical variants in pneumatisation of the sphenoid sinus.[27,28]

Intraoperative Doppler

Doppler is particularly recommended in repeat interventions and giant tumours, or in the case of invasion of the cavernous sinus with distortion of the surgical anatomy.

Intraoperative magnetic resonance imaging

The benefit of MRI is mainly the detection of intrasellar residual tumour, which might have gone undetected during the operation. Intraoperative MRI is not currently implemented in many centres, and its use is not widespread.[29]

Table 3 Preoperative treatment of hormone deficiencies.

Clinical condition	Indications	Treatment guidelines
Administration of glucocorticoids prophylactically or for ACTH deficiency	ADMINISTER IF:	• Prophylactic (protocol by *Inder et al.*[59])
	• Pituitary-adrenal axis not assessed	• Well-adjusted dosing and short treatment regimen for early post-surgical reassessment[59]:
	• Previous AI: serum cortisol 8–9 a.m. < 5 μg/dl or 5–8 μg/dl associated with other pituitary deficiencies or cortisol after ACTH 1–24 test <18 μg/dl*	*Hydrocortisone*:
	• Prior long-term GC therapy	• day -1 (before surgery): 20–40 mg/day oral
	• Total hypophysectomy or section of the pituitary stalk	• day 0 (surgery): induction 50–100 mg iv, followed by 50 mg/8 h iv;
	• Pituitary apoplexy	• day 1: 25 mg/8 h iv
	NOT RECOMMENDED	• day 2: 25 mg po at 8 am and stop
		• days 3–5 reassess basal cortisol
	• Serum cortisol 8–9 a.m. ≥15 μg/dl or after ACTH 1–24 test ≥18 μg/dl*	*Dexamethasone*:
	• Serum cortisol 8–9 a.m. ≥ 9 μg/dl in closely monitored settings[57,58]	• day 0 (surgery): induction 4 mg iv
	• In cases of transsphenoidal selective adenomectomy	• day 1: 2 mg iv/po at 8 a.m.
		• day 3: 0.5 mg iv/po at 8 am and stop
		• days 3–5 reassess basal cortisol
TSH deficiency	• Secondary or primary hypothyroidism	• *Levothyroxine:* 1.4–1.7 μg/kg/day
		• Lower doses in older adults, heart disease and in severe long-standing hypothyroidism[60]
		• Always with prior correction of ACTH deficiency if present
ADH deficiency	• Uncommon in PT, common in lesions with suprasellar extension: craniopharyngiomas and pituitary metastases[61]	• *Desmopressin po*, sublingual, intranasal or iv (equivalents: 200 μg po = 120 μg sublingual = 10 mg intranasal = 1 μg iv)
GH deficiency	• No treatment recommended	• No treatment recommended
FSH/LH deficiency	• Consider treatment if surgery will be significantly delayed and the patient is symptomatic	• Males: Testosterone im; testosterone undecanoate (1000 mg every 10–14 weeks); testosterone cypionate (100–250 mg every 2–4 weeks). Transdermal testosterone: testosterone gel (50 mg/day).
		• Females: oral or transdermal oestrogens. Combine with progestogens if uterus intact

ACTH: adrenocorticotropic hormone; ADH: antidiuretic hormone; FSH: follicle-stimulating hormone; GC: glucocorticoids; GH: growth hormone; AI: adrenal insufficiency; im: intramuscular; iv: intravenous; LH: luteinising hormone; po: oral; PT: pituitary tumour; sc: subcutaneous; TSH: thyroid-stimulating hormone.

* It is recommended to establish reference cut-off points for the study population at each centre. Higher cut-off points (usually >21 μg/dl) should be considered in patients on oral hormonal contraceptives.[62]

Intraoperative complications

Focusing on the transsphenoidal approach, the main complications and their impact are detailed in Table 4.

Surgical report

The surgical report should include: 1) the approach route; 2) a description of the complete surgical technique in its different phases; 3) a description of the lesion; and 4) the closure technique used. Table 5 shows an example of a basic report.

Collection and dispatch of samples for pathology and tissue banking

The standardised histopathology report is essential for classifying the type of lesion and will help adapt subsequent treatments and predict how the lesion may behave in the future.[30]

Postoperative monitoring

There are two distinct stages in the postoperative phase: the first covers the day of surgery and the first 24 h, and the second is the transfer of the patient to the ward.

Table 4 Intraoperative complications.

	Complication	Consequence/Treatment
Transsphenoidal approach		
Nasal phase	Loss of nasal structural support (more common in extended procedures)[63]	Nasal deformity
	Sphenopalatine artery or posterior septal artery lesion	Epistaxis. Requires cauterisation or occlusion with vascular clips[64]
	Septal and/or mucosal perforation	Crusting, dry nose, bleeding/epistaxis
Sphenoidal phase	Carotid artery injury (incidence 0.2%—0.4%)	Severe neurological complication[65] Stabilisation of the patient by anaesthesia Requires immediate local treatment: packing, sealing, clipping[66] Requires urgent endovascular assessment: embolisation, arterial closure or reconstruction
	Accidental opening of the skull base in the removal of intrasphenoidal septa	Intraoperative CSF fistula, requiring nasoseptal flap repair
	Vidal nerve injury	Ipsilateral soft palate dysaesthesia, nose and eye dryness
Sellar phase	Cranial nerve damage[67]	Paresis or paralysis
	Intraoperative CSF fistulas	- Low-flow fistulas: reconstruction with dural substitutes + fascia lata/fat. - High-flow fistulas: nasoseptal flap reconstruction[68]
	Injury to anterior or posterior pituitary, chiasm, hypothalamus. Difficult haemostasis with bleeding in invasive lesions	Hypopituitarism, visual deficit, hypothalamic syndrome
Transcranial approach		
• Optical damage due to surgical manipulation.		
• Injury to the hypothalamic perforating arteries. Injury to the carotid arteries and their branches.		
• Cranial nerve lesions: parasellar tumours with invasion of the cavernous sinus.		

CSF: cerebrospinal fluid.

Day of surgery and first 24 h in the Post-Anaesthesia Recovery/High Dependency Unit

Management in the preoperative and immediate postoperative period is described in Table 6.

Transfer to the hospital ward

In general, the patient can be transferred to the ward within 12—24 h after the operation. On the ward, vital signs, including fluid balance, are usually checked every eight hours. The venous access, fluid therapy and urinary catheter can be removed after 24—36 h. Electrolytes, including sodium, plasma osmolality, urine osmolality, and specific gravity, can be spaced every 12—24 h depending on the patient's clinical status and fluid balance. At 48—72 h, it is advisable to do a pituitary profile to check for the appearance of new hormone deficiencies and to guide the assessment of remission and/or persistence of the disease in functioning PT, along with the rest of the examinations[31–33] (Table 7).

For venous thromboembolism prophylaxis after surgery, external elastic compression stockings, elevation of the lower limbs and encouraging early mobilisation (avoiding Valsalva manoeuvres) can avoid the routine use of subcutaneous heparin.[31,34] Management of the patient on the ward is summarised in Table 7.

Postoperative neurosurgical complications

The main complications in the immediate postoperative period and their management are described in Table 8.

Early postoperative hormone testing

Surgery can restore pituitary function in up to 30% of patients with pre-existing hypopituitarism, but induces new hormone deficiencies in 2%–15% of cases.[35] In Cushing's disease, up to 25% of cases develop some degree of hypopituitarism due to the increased pituitary manipulation during surgery and the medial location of the corticotropinomas.

Immediate postoperative assessment of anterior pituitary function

Clinical assessment of the patient and determination of morning plasma cortisol is the most commonly used and most straightforward test to assess the integrity of the hypothalamic-pituitary-adrenal (HPA) axis. A morning cortisol value 72 h after surgery of less than 2.1 μg/dl (<60 nmol/l) is indicative of post-surgical AI. In contrast, in patients without previous ACTH deficiency and after selective pituitary surgery, a value above 9.7 μg/dl (>270 nmol/l) suggests adrenal sufficiency.[36] In the postoperative period,

Table 5 Contents of the report following pituitary tumour surgery.

Type of approach		
• *Transsphenoidal*	Description:	Remarks
◯ Endonasal endoscopic	• Sellar	
◯ Microscopic	• Expanded	
• *Transcranial*	◯ Transtuberculum/transplanum	
	◯ Transcavernous	
	◯ Transclival	
Surgical technique		
Nasal phase		
Structures resected	• *Middle turbinate (uni/bilateral)*	
	• *Partial/complete ethmoidectomy (uni/bilateral)*	
	• *Post/anterior septum (perforations)*	
Intrasellar phase		
Extent of resection	■ Intracapsular	Arterial Bleeding
■ Total	■ Extracapsular	■ Yes
■ Partial	Carotid artery unroofing (left/right)	■ No
■ Intentional residual tumour	■ Yes	Venous Bleeding:
Site:	■ No	■ Yes
Justification:	Diaphragma sellae opening:	■ No
■ CSF leak	■ Yes	
■ Nerve damage	■ No	
Description of pituitary tumour	Consistency	
	Vascularisation	
	Left cavernous sinus invasion: Yes. No	
	Right cavernous sinus invasion: Yes. No	
	Normal gland: Yes No	
	Cleavage plane	
	■ Gland	
	■ Neighbouring structures	
*Intra-arachnoid phase**		
Dissection planes		
Adherence to structures		
Relationship to the 3rd ventricle		
Reconstruction closure		
• Free flap	• Middle turbinate mucosa	• Dural patch
• Pedicle flap	• Nasoseptal (left/right), lateral wall	• Sealant
• Synthetic materials	• Lower turbinate (left/right)	• Probe
• Autologous materials	• Fat	• Nasal packing
	• Fascia lata	
Systemic events		
• Allergic reactions		
• Airway difficulty		
• Cardiorespiratory instability		
• Vagal, hyperactivity of the vagus nerve		

* In case of adenoma with arachnoid invasion or craniopharyngiomas.

neither ACTH stimulation (Synacthen®) nor insulin-induced hypoglycaemia help assess the HPA axis.

The diagnosis of central hypothyroidism is biochemical and is characterised by reduced levels of free thyroxine (FT4) along with inappropriately low, normal or mildly elevated TSH. After surgery, levothyroxine treatment is recommended if FT4 levels drop by 20% or if the patient develops symptoms.[35]

GH, FSH and LH deficiencies are not assessed in the immediate postoperative period, as recovery may be delayed for more than a year.

Assessment of postoperative pituitary function in the immediate postoperative period: fluid and electrolyte complications

Hyponatraemia

The diagnostic tests for hyponatraemia and the diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are summarised in Table 9.

Most neurosurgical hyponatraemia tends to be mild. However, moderate/severe hyponatraemia (sodium <120 mmol/l or drop of over 10 mmol/l in 48 h) is the most common cause of readmission to the hospital after surgery. The main treat-

Table 6 Day of intervention and first 24 h in the Post-Anaesthesia Recovery/High Dependency Unit.

Preoperative and intraoperative	• Review of previous treatments (for example, antihypertensive, antiangina, antiarrhythmic and bronchodilator) to be administered according to general intracranial surgery protocols.[69] • Assessment of the need for perioperative corticosteroid coverage. • Management of hyperglycaemia and diabetes using standard hospitalisation protocols. Discontinuing oral hypoglycaemic agents the day before surgery is recommended. • Cannulate two peripheral venous lines for conventional fluid therapy (consider central line in cases of high surgical risk [expanded approaches]) • Bladder catheterisation: hourly fluid balance. • Anti-emetic prophylaxis: In 40% of cases, nausea or vomiting can increase intracranial pressure.[70] • Antibiotic prophylaxis. • Pain treatment: NSAID, opioids in second line and with particular caution in patients with SAHS. • Avoid long-acting sedatives that interfere with assessing the patient's neurological status.
Postoperative	*Transfer of the patient to the ICU in the case of*[34]*:* • Giant lesions with significant suprasellar extension requiring a complex and prolonged approach. • Serious surgical complications. • Serious medical comorbidities. *Checks (first 2–24 h postoperatively)* • Hourly: vital signs (HR, BP, Temp.), diuresis and fluid balance • Every 6–12 h: plasma and urinary sodium and osmolality, urine specific gravity • Every 24 h (first 72 h): basal plasma cortisol

BP: blood pressure; DM2: diabetes mellitus type 2; HDU: Post-Anaesthesia Recovery/High Dependency Unit; HR: heart rate; ICU: intensive care unit; NSAID: non-steroidal anti-inflammatory drug; SAHS: sleep apnoea hypopnoea syndrome; Temp.: temperature.

ment strategies are: fluid restriction; avoiding excessive postoperative fluid therapy; and encouraging self-regulation (drinking according to thirst).

The administration of 3% hypertonic saline (3%HS) should be reserved for moderate-to-severe (<125 mmol/l) and/or symptomatic hyponatraemia. The recommendation is to infuse 3%HS at a rate of 0.5–2 ml/kg/h or give 3%HS boluses at doses of 2–4 ml/kg (100–150 ml) every 20–40 min, to increase plasma sodium by no more than 8 mmol/l in 24 h to reduce the risk of osmotic demyelination.[35,37,38]

Diabetes insipidus (vasopressin deficiency)

Transient diabetes insipidus (DI) is the most common complication of pituitary surgery. Polyuria is the most obvious symptom and may be due to several factors: excessive fluid therapy; excessive fluid intake due to nasal packing; high-dose GC coverage; or Cushing's disease and acromegaly, in which the decrease in cortisol and GH will result in a negative fluid balance in the first 48 h after surgery. The diagnosis of DI is based on clinical and laboratory findings (Table 10).

The goal of DI treatment is to ensure that osmotic homeostasis is maintained. It is recommended that the patient follows a ''fluid hygiene'' regimen (drinking when thirsty). If the patient is unable to replace urinary losses orally, fluid therapy should be continued to maintain fluid balance. Drug treatment with desmopressin should be conditional on the patient suffering form polyuria-polydipsia with negative fluid balance or hypernatraemia.

Immediate assessment by magnetic resonance imaging

Early MRI (24–48 h post-intervention) can be useful to assess the tumour resection, detect residual disease, evaluate gland and pituitary stalk preservation (anticipate possible deficiencies), and to assess the possible need for early re-intervention or plan adjuvant therapy.[39,40]

Medical treatment and discharge recommendations

A joint report by neurosurgery and endocrinology is recommended in conjunction with the nursing discharge report. It should include general (Table 11) and individual recommendations according to postoperative hormone status, risk of hyponatraemia, type of surgical approach and development of intraoperative CSF leaks.

Postoperative assessment and follow-up

The recommended follow-up is summarised in Fig. 1 and includes the following visits.[31]

One to two weeks after surgery (check-ups by Endocrinology and Ear, Nose and Throat)

- Baseline assessment of the adrenal axis: adjustment/withdrawal of treatment and reinforcement action plans for ''sick days'' in patients with AI.
- Fluid balance and electrolytes.
- Assessment of possible postoperative complications.

Four to six weeks after surgery (check-ups by Endocrinology, Neurosurgery and Ear, Nose and Throat)

- Review of the pathology report.

Table 7 Immediate perioperative timetable.

	Intervention day	First 12—24 h	WARD day 1	WARD day 2	WARD day 3	DISCHARGE
Visit	NS ENT Anaesthetics Endo[a]	ICU/HDU NS Endo[a]	NS Endo ENT[b]	NS Endo ENT[b]	NS Endo ENT[b]	NS Endo ENT[b]
Fluid therapy	Premedication and hormone treatment if required	YES	Assess and withdraw fluid therapy and venous access (24—36 h)			Discharge Report
Peripheral/central line	YES	YES				- NS - Endo - Nursing
Antibiotic prophylaxis	YES	YES	YES	YES	Discontinue after removal of plugs	
Urinary catheter (UC)	UC placement	YES	Assess removal (24—36 h)			
Neurological Care and Monitoring	YES	YES	YES	YES Assess removal of nasal packing	YES Assess removal of nasal packing	
Vital signs (HR, BP and Temp.)	Times	Times	Every 8 h	Every 8 h	Every 24 h	
Diuresis and fluid balance	Times	Times	Every 8 h	Every 24 h	Every 24 h	
Sodium/Plasma osmolality	Every 6—12 h	Every 6—12 h	Every 12—24 h	Every 24 h	Every 24 h	Prior to discharge
Sodium/osmolality/urine density	Every 6—12 h	Every 6—12 h	Every 12—24 h	Every 24 h	Every 24 h	
Plasma cortisol 8 a.m.[c]		YES	YES	YES		
Hormonal profile			YES			
Oral tolerance		YES	Move onto diet	Normal diet	Normal diet	Normal diet
DVT prophylaxis (LMWH): High risk (Cushing's) and non-mobilisation only			YES	YES	YES	
Mobilisation		Rest	Rest/start mobilisation	Effortless free activity (no Valsalva)	Effortless free activity (no Valsalva)	Effortless free activity (no Valsalva)
Other care:						
- Prevent constipation and treat nausea/vomiting.	YES	YES	YES	YES	YES	
- Pain control	YES	YES	YES	YES	YES	
- Close monitoring for signs/symptoms of hypocortisolism		YES	YES	YES	YES	YES

a.m.: before noon; BP: blood pressure; DVT: deep vein thrombosis; Endo: endocrinology; ENT: ear, nose and throat specialist; HDU: Post-Anaesthesia Recovery/High Dependency Unit; HR: heart rate; ICU: intensive care unit; LMWH: low molecular weight heparin; NS: neurosurgery; Temp.: temperature.

[a] Recommended.

[b] Optional, not always possible.

[c] Patient without 24-48-72 h glucocorticoid coverage curve.

Table 8 Early postoperative complications, incidence and management.[66,71,72]

Complications	Incidence	Management
Sinonasal	0.24%—4.8%	- Significant epistaxis: stabilisation and tamponade, urgent surgical re-exploration. - Perform urgent cerebral arteriogram or CT angiogram in case of suspected ICA injury.
CSF fistula	1.1%—3%	- Assess after removal of tamponade: sample nasal exudate fluid for determination of β-trace or β2-transferrin.[73,74] - Early surgical closure +/- lumbar drainage (BMI > 25 kg/m2 or high flow).
Meningitis	0.3%—2.1%	Fistula treatment, lumbar puncture and antibiotic therapy (vancomycin + cefepime/ceftazidime/meropenem)
Acute hydrocephalus Hypertensive pneumoencephalus	0.8%—1.6%	ICU, EVD
SAH Vasospasm	0.1%—0.7%	ICU, medical treatment: euvolemia, prevent hypotension, nimodipine
Visual - Visual acuity, diplopia	0.3%—4%	- Urgent brain CT scan: reintervention in case of sellar haematoma. - Short course of dexamethasone (if secondary to surgical manipulation).

BMI: body mass index; BP: blood pressure; ESV: external ventricular drain; ICA: internal carotid artery; ICU: intensive care unit; SAH, subarachnoid haemorrhage.

Table 9 Differential diagnosis of hyponatraemia after pituitary tumour surgery (*adapted from Garrahy et al.*[37]) and SIADH diagnostic criteria.

Differential diagnosis of postoperative hyponatraemia			
Sodium in urine	Hypovolaemic	Euvolaemic	Hypervolaemic
<20 nmol/l	Dehydration	SIADH with fluid restriction	- Excessive fluid intake - Congestive heart failure - Cirrhosis - Chronic kidney disease - Desmopressin overdosage
>40 nmol/l	Adrenal insufficiency	SIADH: 3—12 days after surgery. Incidence 4%—20%[35]	
	Cerebral salt wasting: hyponatraemia accompanied by volume depletion, natriuresis and a response to intravenous saline	SIADH Diagnostic criteria[38,75,76]	
	Other: diuretics, renal salt wasting	• Blood sodium <135 mmol/l • Plasma osmolality <275 mOsmol/kg • Osmolality of urine >100 mOsmol/kg • Urinary sodium >40 mmol/l (with normal salt and water intake) • Euvolemia • Exclusion of glucocorticoid and thyroid hormone deficiency Adrenal insufficiency Central hypothyroidism Hypopituitarism	

SIADH: syndrome of inappropriate antidiuretic hormone secretion.

- In functioning tumours with probably incomplete excision, functional evaluation of hypersecretion is to determine the initiation of medical treatment.
- Assessment of the adrenal axis and thyrotropin
- Assessment of possible postoperative complications.
- Ear, Nose and Throat
- Request follow-up MRI

Three to six months after surgery (check-ups by Endocrinology, Neurosurgery, Ophthalmology and Ear, Nose and Throat)

Full assessment to include:

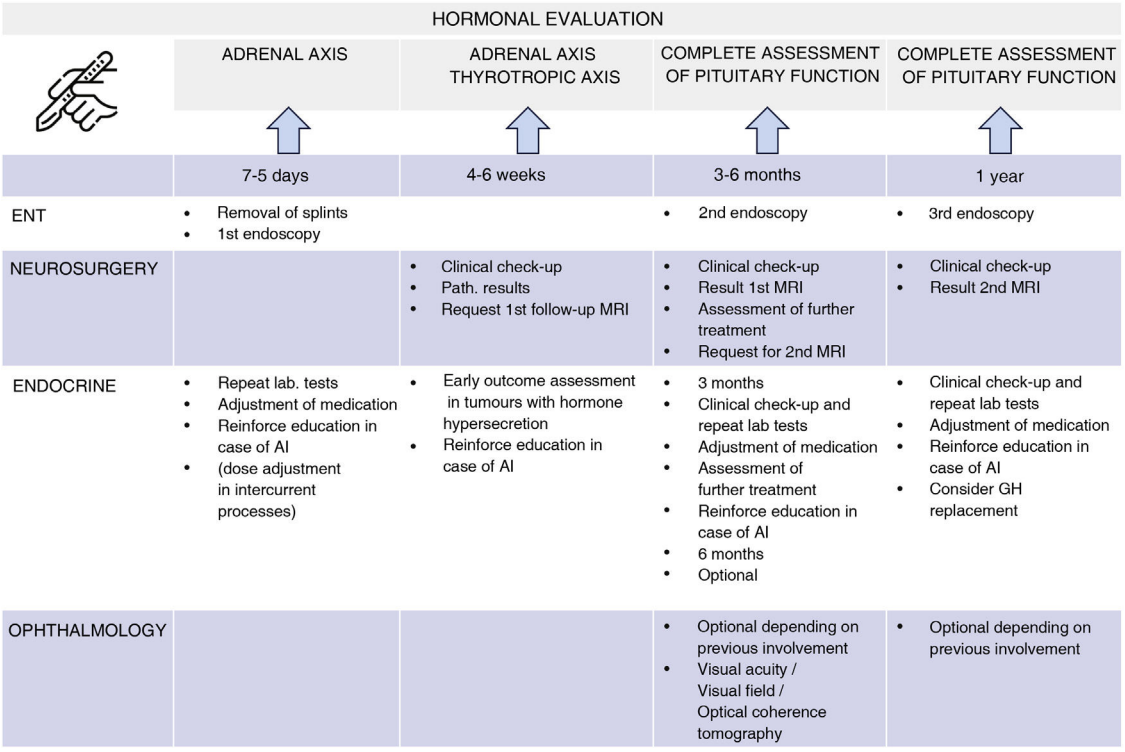

Figure 1 Postoperative multidisciplinary follow-up schedule for the patient with a pituitary tumour. Recommended times for medical check-ups, hormone determinations and evaluation of imaging tests.
AI: adrenal insufficiency; GH: growth hormone; MRI: magnetic resonance imaging; Pa: pathology.
* whenever there is visual impairment. ** The evaluation of GH deficiency replacement is not considered until one year after surgery, once stability and correct supplementation of the rest of the pituitary axes have been confirmed.

Table 10 Definition of diabetes insipidus (DI) after pituitary surgery (adapted from *de Vries et al.*).[77]

Definition of postoperative DI
Hypotonic polyuria • ≥300 ml/h or >4 ml/kg/h × 2 consecutive h (3 h if closely monitored) • urine specific gravity <1005 or urine osmolality <100 mOsm/kg Plus at least some of the following criteria: • Excessive polydipsia • Plasma osmolarity >300 mOsm/kg • Hypernatraemia (Sodium >145 mEq/l)

Table 11 Discharge recommendations after pituitary surgery.[34,75,77–79]

Discharge recommendations:
- Fluid hygiene: Drink only if thirsty - Fluid restriction: 1 l/day for 1 week (in selected patients) - Nasal saline nasal spray every 12 h - Be aware of symptoms of adrenal insufficiency or hyponatraemia (anorexia, nausea, asthenia, hypotension and drowsiness) - Be aware of symptoms of diabetes insipidus (excessive polydipsia, inappropriate polyuria, nocturia) - Be aware of symptoms of suspected meningitis or CSF fistula (fever, severe headache, stiff neck, CSF rhinorrhoea) - Avoid Valsalva manoeuvres for at least the first month - In cases of sleep apnoea, do not use CPAP until healing of the nasal mucosa (4—6 weeks) - Avoid steam baths or saunas, submerging the head or travelling by plane
CPAP: continuous positive airway pressure: CSF: cerebrospinal fluid.

- Complete hormone profile of pituitary function with specific assessment of biochemical normalisation in functioning tumours, assessment of recovery or loss of pituitary function (Table 12).
- Basic blood tests with electrolytes, glucose/HbA1c and in patients with fluid and electrolyte imbalance or DI, plasma osmolarity, urine volume, urine osmolarity and urine Na^+/K^+.
- Neurosurgery check-up: clinical and postoperative MRI assessment.
- Ophthalmology re-assessment in the case of previous defects.
- Ear, Nose and Throat check-up as required.

Twelve months after surgery

Full hormone measurements including somatotropic axis; at this time the need for GH replacement is assessed; request for a new MRI (Fig. 1).

Table 12 Postoperative assessment of the adenohypophysis.

	Diagnosis	Treatment and monitoring	Comments
Central adrenal insufficiency (AI)	Screening:	Treatment:	• AI treatment can unmask central DI
	-Serum cortisol 8–9 a.m. and plasma ACTH before taking morning GC *Normal laboratory results do not rule out a diagnosis of AI*	GC in general hydrocortisone 15–20 mg/d divided in 2 or 3 intakes Follow-up:	• Patient and family training for sick daysör times of intercurrent disease The Synacthen® test should not be performed before six weeks postoperatively (the adrenal gland requires time to destructure in the absence of ACTH).
	Confirmation:	Monitoring of steroid replacement therapy is not analytical (neither basal cortisol nor ACTH). It is based on the patient's clinical condition and the monitoring of body weight, blood pressure and quality of life.	
	4–6 weeks postoperatively Use one (or more) of the following: • ACTH stimulation test for cortisol • Insulin-induced hypoglycaemia test		
Central hypothyroidism	Screening:	Treatment:	• Serum TSH is not useful in the follow-up of central hypothyroidism
	Serum TSH and FT4	Titrate FT4 every 6–8 weeks up to a maintenance dose (usually around 1.6 μg/kg).	• Rule out AI before starting levothyroxine (FT4 enhances cortisol clearance and may cause adrenal crisis).
	6–8 weeks postoperatively	Follow-up: serum determination of FT4 with the aim of maintaining levels in the middle/upper half of the reference range.	
Central hypogonadism	Screening:	Treatment:	• Regular menses in the absence of hormonal treatment or contraceptives rules out hypogonadism
	Serum LH, FSH, total testosterone, prolactin (in men) and oestradiol (in premenopausal women)	• Males: testosterone if fertility is not desired.	• The transdermal route of oestrogen interferes less in the case of concurrent GH replacement therapy (the oral route reduces peripheral sensitivity to GH).
	Confirmation:	• Females: oestrogens if fertility is not desired. Add progestogens if the patient has an intact uterus.	• CD and hyperprolactinaemia may cause hypogonadism per se. Therefore, biochemical assessment of central hypogonadism should not be performed until several months after confirmation of surgical success (the effects of hypercortisolism may remain longer term).

Table 12 (*Continued*)

	Diagnosis	Treatment and monitoring	Comments
	3 months postoperatively • In males: a second testosterone determination may be necessary, in addition to SHBG and bioavailable testosterone in selected cases	Follow-up: Males: total testosterone, PSA and haematocrit	
		Females: the presence of regular menstruation indicates an adequate oestrogen level for replacement therapy. Serum oestradiol and FSH level are optional • Gonadotrophins: fertility treatment monitoring	
Adult GH deficiency	Starting GH therapy in patients with no previous deficiency is not considered until one year after surgery, always with other associated deficiencies in pituitary function and no significant residual tumour.	Treatment:	•GH treatment can unmask AI or central hypothyroidism.
	Screening:	rhGH	• Rule out AI: rhGH blocks the conversion of cortisone to cortisol
	Serum IGF-1	Start with low doses 0.15—0.3 mg/day	• Rule out central hypothyroidism:
	Confirmation:	Maintenance dose, 0.15—1 mg/day	◯ rhGH can lower free T4
	• Not required if 3 axes are affected.	Follow-up:	◯ leads to false negatives in dynamic tests
	• Insulin-induced hypoglycaemia	• Target serum IGF-1 in the upper half of the age-adjusted reference range.	• Fertile (oestrogenic) females generally require a higher dose of GH than males
	• GHRH + arginine stimulation	• Quality of life, body weight, glucose, waist circumference and blood pressure are also important parameters	
	• Glucagon stimulation		

ACTH: adrenocorticotropic hormone; AI: adrenal insufficiency; CD: Cushing's disease; DI: diabetes insipidus; FSH: follicle-stimulating hormone; FT4: levothyroxine; GC: glucocorticoids; GH: growth hormone; GHRH: growth hormone-releasing hormone; IGF-1: insulin-like growth factor type 1; LH: luteinising hormone; rhGH: recombinant human growth hormone; SHBG: sex hormone-binding globulin; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone.

Table 13 Monitoring criteria in functioning pituitary tumours.

	Cure/monitoring criteria
Cushing's disease	Transient AI after pituitary surgery indicates remission Basal cortisol at 8 a.m.: usually performed 1—7 days postoperatively (prior to morning GC administration) √ Remission very likely, basal cortisol <50 nmol/l (1.8—2 μg/dl) √ Remission likely, cortisol <138 nmol/l (5 μg/dl) √ Persistent disease likely for values >200 nmol/l (7.2 μg/dl) • The patient may develop ''GC withdrawal syndrome'' immediately after surgery: this can last 6—12 months. It is characterised by AI-like symptoms despite adequate GC replacement therapy. Patients may benefit from the temporary use of higher doses of GC, or a slower tapering of oral replacement doses in the postoperative period.

Table 13 (*Continued*)

	Cure/monitoring criteria
	• After recovery of postoperative AI, plasma and urinary ACTH and cortisol levels will be normal. • MRI 3–6 months and yearly if there is residual tumour.
Acromegaly	Early assessment GH, there are no set cut-off points. • IGF-1 at 6 weeks can be useful in many cases • A normal IGF-1 value and an undetectable GH value indicate surgical remission. • If GH is detectable (i.e. >0.4 g/l [if measurement is performed with ultra-sensitive methods] or >1 g/l [for less sensitive methods]), GH measurement after glucose challenge can provide important information[12] and is recommended if GH is >1 g/l. • MRI 3–6 months and yearly if there is residual tumour.
Prolactinoma	• A serum prolactin <10 ng/mL on postoperative day 1 predicts early and subsequent biochemical remission.[80] • Reassess basal prolactin and other axes (especially gonadotropic) 12 weeks after surgery. • MRI 3–6 months and yearly if there is residual tumour.
TSHoma	• Normalisation of T4. • TSH normalisation or prolonged suppression even with central hypothyroidism. • MRI 3–6 months and yearly if no residual tumour

ACTH: adrenocorticotropic hormone; AI: adrenal insufficiency; GC: glucocorticoids; GH: growth hormone; IGF-1, insulin-like growth factor type 1; MRI, magnetic resonance imaging; T4: thyroxine; TSH, thyroid-stimulating hormone (thyrotropin); TSHoma: thyrotropinoma.

Monitoring/cure criteria in pituitary tumours

Cushing's disease

The development of transient central AI after pituitary surgery is an indicator of cure and/or remission.

There is no consensus on the postoperative basal cortisol cut-off point for establishing remission/cure, or on the exact time to test. Hydrocortisone replacement therapy should be started when serum cortisol is below 5.0 μg/dl or patients show symptoms of AI (Table 13).

Even in patients in remission after pituitary surgery, follow-up has to be long-term because of the possibility of long-term recurrence (reported in 5%–35% of patients)[19] and for the management of post-Cushing's syndrome.

Acromegaly

Different GH levels on the first day after surgery,[41–43] even at six hours,[44] have been proposed as predictors of remission. The IGF-1 concentration at six weeks after surgery is often used to assess remission.[45] In some cases with slightly elevated levels at six weeks, IGF-1 concentration may return to normal within three to six months.[46] Therefore, determining basal GH and IGF-1 from 12 weeks and adding a GH test after oral glucose challenge in patients with GH levels >1 μg/l is of particular importance[12,47,48] (Table 13).

Prolactinoma

In routine clinical practice, functional evaluation (prolactin, pituitary function, especially gonadotropic axis) and assessment by imaging are performed from 12 weeks after surgery. Depending on the results, the need for additional treatment is assessed according to the histological diagnosis and the criteria for tumour aggressiveness.

Thyrotropinoma

In the case of surgical cure, central hyperthyroidism is corrected, and postoperative TSH is usually undetectable or low for weeks or even months.[49] It can lead to transient or permanent central hypothyroidism, whether due to prior tumour compression of the pituitary gland and normal thyrotropic cells or surgical damage. In these cases, FT4 replacement therapy is necessary.

Non-functioning tumour

Hormone testing to assess for recovery or loss of pituitary function is usually performed two to three months after surgery. Postoperative radiological monitoring is essential in non-functioning PT due to the lack of a hormone marker and early clinical symptoms to warn of progression.[50]

In general, MRI for evaluation of remnants will be performed at three to six months. The next follow-up is annual, and both MRI serve as a reference for subsequent follow-up.[50]

When there is no residual tumour or the verdict is uncertain, MRI is repeated annually for five years and then at seven, 10 and 15 years.[50,51] Conversely, when there is a residual tumour or suspicious images are identified, MRI is repeated annually for five years and then every two to three years in the absence of progression, adjusting the schedule on a case-by-case basis according to the size of the tumour, its progression and the distance to the visual pathways.

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Author contribution

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Conflicts of interest

None of the authors has any conflicts of interest to declare in relation to the content of this article.

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