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Anglia Cancer Network

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Anglia Cancer Network

Regional Guidelines for the Management of Pituitary Tumours

Pituitary Network Site Specific Group (NSSG)

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1.0 Introduction

1.1 Purpose of these guidelines

Pituitary tumours represent a heterogeneous group of disorders, both clinically and pathologically. These guidelines relate to the management of patients with all types of pituitary tumour whose care falls under the Anglia Cancer Network (ACN) Pituitary Site Specific Group. Where available, they are consistent with international guidelines/consensus statements, taking into consideration local issues, and developed in line with the practices of the long-standing Cambridge Pituitary MDT. They are not intended to offer a rigid protocol, but to provide a framework for the delivery of high quality specialist care in the Eastern Region.

2.0 Pituitary tumours

2.1 Introduction

Pituitary tumours are common with an estimated prevalence of 16.7% in the general population (Ezzat and colleagues – systematic review, 2004)(1)(see below). Although the majority of these lesions are clinically silent, a subgroup of patients manifest endocrine and/or neurological sequelae due to one or more of: (i) hormone hypersecretion, (ii) hypopituitarism, (iii) local mass effect (e.g. optic chiasm compression). Most pituitary tumours are pituitary adenomas (PA): based on size, PA are traditionally classified as microadenomas (<1 cm maximum diameter) or macroadenomas (>1 cm maximum diameter), each of which may be either hormone-secreting (i.e. functional) or non-functional (non-functioning pituitary adenomas – NFPA). Common functional tumours secrete prolactin (PRL – prolactinomas), growth hormone (GH – somatotropinomas – acromegaly) or adrenocorticotrophic hormone (ACTH – corticotropinomas – Cushing's disease). Tumours secreting thyroid stimulating hormone (TSH), or biologically active follicle stimulating hormone (FSH) and/or luteinizing hormone (LH) are rarer.

2.2 Epidemiology

Both autopsy and radiological series indicate that pituitary tumours are common: 14.4% prevalence at autopsy (systematic review of 3375 subjects in 7 studies)(1); mean prevalence in radiological series 22.3% (systematic review of 202 subjects in 3 studies)(1); yielding a 'combined final prevalence' of 16.7%(1). The majority of these tumours are clinically silent. Clinically relevant PA (i.e. those presenting with hyperfunction, hypopituitarism and/or mass effect) have been estimated to occur in 1:1000 to 1:1500 of the general population(2, 3). Pituitary tumours account for ~10% of all diagnosed intracranial tumours (Cancer Registry data) and are the third most common intracranial neoplasm(4). Overall the sex incidence is equal, but with a difference for certain tumour types (e.g. microprolactinomas are more commonly diagnosed in women and macroprolactinomas

are more common in men). Prolactinomas are the most common PA in subjects <60 years, and NFPA in those >60 years. There is no known racial difference in prevalence.

These tumours are rare in childhood and prevalence increases with age (5).

2.3 Aetiology

The majority of pituitary tumours are benign PA; pituitary carcinomas are extremely rare (0.2% of surgically resected specimens)(6, 7). Although there have been recent advances in the understanding of the aetiopathogenesis of pituitary tumours, knowledge of the cellular mechanisms underlying tumour development in most patients remains sparse. Factors implicated in pituitary tumorigenesis include those intrinsic to the pituicyte, and altered availability of regulatory factors and autocrine/paracrine growth factors(8). Evidence suggests that pituitary tumours arise as a result of monoclonal expansion of a single transformed cell, rather than polyclonal proliferation(8). The occurrence of mixed plurihormonal tumours originating from primitive pluripotent progenitor cells further supports a *de novo* origin for these tumours(8). Growth factors may play an important role in promoting the growth of the already transformed pituitary cell. Most PA are sporadic tumours, but a small proportion may have an underlying genetic cause (see below).

2.4 Genetics

It is estimated that pituitary tumours arise in a familial setting in approximately 4 to 5% of cases. Currently, four conditions are known to be associated with familial pituitary tumor syndromes (Table 1): multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 4/type X (MEN-4/MEN-X), Carney complex (CNC) and familial isolated pituitary adenomas (FIPA)(9). Over half of these familial cases are due to MEN-1 or CNC(3). Prolactinomas predominate amongst MEN-1 associated PA, and are typically macroadenomas (~80%), with higher rates of invasion than in non-MEN-1 prolactinomas – their response to dopamine agonists is often poor, with <50% of cases exhibiting normalisation of serum prolactin(10). Other pituitary tumours also tend to be larger and more aggressive in MEN-1(10). A small number of patients with *CDKN1B* gene mutations have been identified with PA, hyperparathyroidism and a variety of other tumours, although it remains unclear whether the latter are core features of this syndrome (MEN-4/MEN-X)(11, 12). Approximately 10% of patients with CNC manifest overt acromegaly, which often develops insidiously(13); others (~75%) exhibit asymptomatic elevations in GH/IGF-1 ± prolactin levels, or abnormal responses to dynamic pituitary testing. A distinguishing feature of CNC-related acromegaly is multifocal hyperplasia of somatomammotrophic cells(14). A significant proportion of the remaining familial cases fall in to the FIPA category(15, 16), which differ from sporadic tumours

in that they tend to occur at younger age and often present with larger tumours. Germline mutations in the aryl hydrocarbon receptor-interacting protein gene (*AIP*) are found in ~15% of families (16). In FIPA, pituitary tumours of the same type can occur in all affected family members, or different types of tumour may be seen. The frequencies of the various different PA in FIPA are estimated as: prolactinomas ~40%; somatotropinoma ~30%; NFPA ~13%; somatolactotropinoma ~7%; gonadotropinoma ~4%; corticotropinoma ~4%; thyrotropinoma ~1%(3). Macroadenomas make up nearly two thirds of diagnosed PA in FIPA patients. Prolactinomas are generally more invasive than in sporadic disease(3).

If a familial pituitary tumour syndrome is suspected, consider (i) referring to the East Anglian Genetics service for advice on screening (ii) entering the patient into the UK FIPA study coordinated by Professor Marta Korbonits (St. Bartholomew's Hospital, London) (Several hospitals in East Anglia (Cambridge, Ipswich, Norfolk & Norwich) are already registered as participating centres).

Disorder	**Key clinical features**	**Gene/locus**
Multiple endocrine neoplasia type 1 (MEN-1)	• Parathyroid hyperplasia • Pituitary tumours (~40%) • Enteropancreatic tumours • Lipomas, angiofibromas, collagenomas	• *Menin* (Chromosome 11q13)
Carney complex (CNC)	• ACTH independent Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD) • Acromegaly – pituitary adenoma/hyperplasia • Thyroid tumours/nodules • Testicular neoplasms [large cell calcifying Sertoli cell tumours (LCCSCT); Leydig tumours) • Myxomas • Spotty skin pigmentation	• *PRKAR1A* (~60%) (Chromosome 17q22-24) • ? gene (Chromosome 2p16)
Multiple endocrine neoplasia type 4/X (MEN-4/MEN-X)	• Pituitary tumours – often GH secreting • Parathyroid hyperplasia • ± ? benign kidney tumours, testicular malignancy, carcinoid tumours	• *CDKN1B* (Chromosome 12p13)

Disorder	Key clinical features	Gene/locus
Familial isolated pituitary adenoma (FIPA)	• Pituitary adenomas • Without extra-pituitary manifestations	• *AIP* (~15%) (Chromosome 11q13)

Table 1. Features of familial pituitary tumour syndromes

2.5 Clinical features and differential diagnosis

As outlined above, apart from those pituitary tumours that are discovered incidentally during radiological investigations undertaken for other clinical indications, or as part of a screening programme in familial disorders, the mode of presentation largely depends on whether the tumour is functional or not (17). Functioning tumours often present with symptoms due to specific hormone excess. For example, prolactinomas in premenopausal women may manifest with galactorrhoea, oligo/amenorrhoea and infertility. In men the symptoms are largely related to associated hypogonadism. Likewise somatotropinomas present with features of acromegaly in adulthood and gigantism in childhood/adolescence. Functioning corticotroph PA cause hypercortisolism and Cushing's disease.

In contrast, many NFPA only come to attention when they become large enough to result in compressive symptoms due to suprasellar (optic chiasmal compromise) or parasellar (III, IV, VI cranial nerve deficits) extension(17). Large functioning tumours may similarly cause local mass effects. In addition, interruption of inhibitory dopaminergic tone can result in hyperprolactinaemia and associated symptoms due to 'stalk disconnection' syndrome (see below)(17).

Varying degrees of hypopituitarism may be present either due to compression of the adjacent normal pituitary gland, or as a secondary consequence of hormone hypersecretion (for example, sustained elevation of prolactin or cortisol can lead to suppression of hypothalamic-pituitary-gonadal function). Some patients may present with target organ sequelae of their hypopituitarism (e.g. osteoporosis, infertility).

A small subgroup of patients with PA develop pituitary apoplexy. Classical pituitary apoplexy refers to a syndrome that is characterised by sudden onset of headache, vomiting, visual impairment and reduced consciousness, resulting from haemorrhage and/or infarction of the pituitary gland (18) . Precipitating factors have been identified in up to 40% of cases, and include hypertension, major surgery (especially coronary artery bypass), dynamic pituitary function testing, anticoagulation therapy/coagulopathy, initiation or withdrawal of dopamine agonists, oestrogen therapy, radiotherapy, pregnancy and head injury (18).

Asymptomatic pituitary haemorrhage and/or infarction (sometimes referred to as 'subclinical pituitary apoplexy') may be detected on routine imaging or during histopathological examination.

2.5.1 Who to suspect pituitary disease in?

As outlined above, many patients with pituitary tumours will present insidiously or serendipitously having had an MRI scan for another reason. However, there are certain categories of patients in whom the index of suspicion for a pituitary disorder should be high, and in whom referral to an endocrinologist should always be considered – these include (but are not restricted to):

- Hypogonadotropic hypogonadism (low testosterone or estradiol, with low or 'inappropriately normal' LH/FSH)
- Unusual thyroid function tests [low thyroid hormone level(s) with low or 'inappropriately normal' TSH; or high thyroid hormone level(s) with raised or 'inappropriately normal' TSH]
- Visual field defects (e.g. bitemporal hemianopia or temporal quadrantanopias)
- Unexplained hyponatraemia
- Unexplained weight loss, tiredness/lethargy/malaise, dizziness
- Incidental sellar/parasellar lesion discovered on CT/MRI scan
- Excess sweating, increase in the size of hands and feet, change in appearance (acromegaly)
- Central obesity, proximal myopathy, purple striae, hypertension, impaired glucose tolerance (Cushing's disease)
- Amenorrhoea and galactorrhoea (prolactinoma females)
- Loss of libido, erectile dysfunction, visual field defect (prolactinoma males).

2.5.2 Who requires urgent referral to an endocrinologist?

All patients with visual field defects/cranial neuropathy of possible sellar/parasellar origin, suspected pituitary failure or pituitary apoplexy should be referred for urgent assessment.

2.5.3 Craniopharyngiomas and other parasellar lesions

Other conditions may also manifest as sellar/suprasellar/parasellar lesions, causing local mass effects and hypopituitarism (Table 2). The presence of diabetes insipidus (DI) should alert the clinician to the possibility of these other disorders [especially craniopharyngioma, metastasis (e.g. breast, bronchus), autoimmune (lymphocytic) hypophysitis and other infiltrative conditions] as DI is rarely a presenting manifestation of PA.

Craniopharyngiomas often behave unpredictably and require detailed and prolonged follow up, including annual MRI scans for the first five years. Debulking surgery is usually required at first presentation, with appropriate replacement therapy instituted. However, radiotherapy and further surgery are frequently required during long term follow up.

Germ cell tumours usually respond well to chemotherapy and require long term oncology follow up. The treatment and investigation of metastases depends on the underlying malignancy, though pituitary replacement therapy is often required.

Autoimmune and infiltrative conditions must always be discussed at an MDT to help define a precise diagnosis and exclude more serious conditions. Long term management usually consists of standard pituitary replacement therapy.

Rathke's cleft and other cysts always require monitoring, frequently require pituitary replacement therapy, but may not require other treatment.

Cysts	**Tumours**	**Miscellaneous**
Rathke's cleft cyst	Pituitary adenoma	Aneurysm
Arachnoid cyst	Craniopharyngioma	Autoimmune hypophysitis
Epidermoid cyst	Meningioma	Infection
Dermoid	Chordoma	Granulomatous disorders
	Metastasis	Langerhans histiocytosis
	Sarcoma/glioma/Schwannoma/hamartoma	
	Germ cell tumours	

Table 2. Examples of conditions that may present with sellar/suprasellar/parasellar lesions.

2.6 Diagnosis

Establishing the diagnosis of pituitary tumours depends on careful history and clinical examination, targeted endocrine testing, high quality imaging and histopathological assessment of surgically resected specimens.

2.6.1 History

The history should include questions to assess for functionality, hypopituitarism and compressive symptoms. If the history is suggestive of a PA then questioning should include reference to potential familial pituitary disorders (Table 1).

2.6.2 Clinical examination

Similarly, clinical examination is predominantly focussed on looking for evidence of hormone hypersecretion, hormone hyposecretion, and compressive signs (visual deficits, cranial nerve deficits) (see above).

If other disorders are suspected, then the history and examination should be targeted appropriately.

2.6.3 Endocrine testing

Initial evaluation should include baseline blood tests in all patients with suspected pituitary disease:

Baseline 'standard' blood tests:

- Full blood count (anaemia and eosinophilia are associated with cortisol deficiency)
- Urea and electrolytes (hyponatraemia is associated with cortisol deficiency, hypernatraemia may complicate diabetes insipidus)
- Liver function (may aid interpretation of borderline testosterone results)
- Bone profile (useful as a 'biochemical screen' for MEN1)

Baseline pituitary function tests:

- Prolactin (with exclusion of macroprolactin if hyperprolactinaemia confirmed – see below)
- Free T4 (FT4) and thyrotropin (TSH)
- Luteinising hormone (LH), follicle stimulating hormone (FSH),
- 9am testosterone (in men), plus sex hormone-binding globulin (SHBG) if available
- Oestradiol (in women)
- 9am cortisol [+/- adrenocorticotrophic hormone (ACTH)]
- Insulin-like growth factor 1 (IGF-1)
- Paired serum and urine osmolalities (if diabetes insipidus is considered a possibility).

Depending on clinical suspicion and the results of baseline investigations, further endocrine evaluation may be required to confirm/refute evidence of hormone hypersecretion and/or hypopituitarism. Table 3 lists some of the most commonly used investigations.

Disorder	**Investigations**
Acromegaly	Oral glucose tolerance test; GH sampling
Cushing's disease	Dexamethasone suppression testing: overnight, low dose, (± high dose); Diurnal cortisol rhythm/late night salivary cortisol; Urinary free cortisol (UFC); Inferior petrosal sinus sampling (IPSS); Corticotropin-releasing hormone (CRH) test
Thyrotropinoma (TSHoma)	Alpha-subunit (alpha-subunit:TSH molar ratio); Sex-hormone-binding globulin (SHBG); TRH test; L-T3 suppression test

Disorder	Investigations
GH deficiency	Insulin tolerance test; Glucagon stimulation test;
Cortisol deficiency	Insulin tolerance test; Short synacthen® test; Glucagon stimulation test
Diabetes Insipidus	Water deprivation test; Hypertonic saline infusion

Table 3. Examples of Investigations used to confirm/exclude hormone hypersecretion and hypopituitarism.

Urgent assessment required in all patients with confirmed pituitary disease

- Prolactin
- 9am cortisol (interpret with caution in females receiving exogenous oestrogen therapy – see below)
- Visual field assessment
- MRI scan

As first line dopamine agonist therapy is generally preferred in patients with prolactinomas, serum prolactin should be determined urgently in all patients before considering pituitary surgery.

Modest hyperprolactinaemia may be seen with pituitary stalk compression (e.g. due to a NFPA or other lesion causing local mass effect). However, recent studies suggest that serum prolactin in such cases rarely exceeds 2000 mU/L(19).

Other causes of hyperprolactinaemia [e.g. drugs (especially certain antipsychotics), renal failure, stress] should also be excluded before making a diagnosis of prolactinoma or ‘stalk disconnection’ syndrome.

Polyethylene glycol (PEG) precipitation of prolactin should always be performed at baseline to exclude biologically inactive ‘macroprolactin’, which of itself requires no further investigation or treatment.

Occasionally, with very large macroprolactinomas (e.g. giant prolactin-secreting PA) that are producing copious amounts of prolactin, laboratory immunoassays provide a falsely low reading due to the so-called ‘hook effect’, in which the assay antibodies are ‘swamped’ by the large excess of prolactin in the patient’s blood(20). In this situation, serial dilution of the serum sample will reveal a rising prolactin level. Therefore, if there is suspicion that a PA may be a macroprolactinoma (e.g.

extensive/invasive tumour), but the serum prolactin level is normal/only mildly elevated, the laboratory should be asked specifically to perform dilution studies(20).

Cortisol deficiency should also be urgently screened for before considering surgery and can often be excluded/confirmed by measurement of a single 9am cortisol level. If the result is 'indeterminate', and dynamic testing is not practical in the timeframe available, the patient should be assumed to be cortisol deficient, commenced on replacement, and formal assessment deferred until after surgery.

The majority of currently available serum cortisol assays measure total as opposed to free cortisol. Hence, wherever possible, it is necessary to withdraw exogenous oestrogen therapy for six weeks before undertaking assessment for hypo- or hyper-cortisolism in female subjects.

Visual field assessment may be limited to a clinical examination in the urgent setting, but findings should be confirmed with formal visual perimetry once practical.

2.6.4 Imaging

2.6.4.1 MRI Scanning

The current gold standard imaging modality for pituitary tumours is magnetic resonance imaging (MRI) with contrast. Ideally thin sections (e.g. 2mm) targeted to the pituitary fossa in both the sagittal and coronal planes should be performed. T1 weighted sequences before and after intravenous contrast are the main-stay of pituitary imaging(21). T2 weighted images may provide additional useful information in certain settings (e.g. Rathke's cleft cyst). There may be additional benefit in performing the post-contrast MRI sequences in a dynamic fashion (within the first 60 seconds) after contrast injection, especially for patients with Cushing's disease as these tumours are frequently difficult to identify(22). This can help visualise small PA, which typically enhance less than normal pituitary tissue, and this differential enhancement is sometimes best appreciated within the early arterial phase post-contrast injection(22).

2.6.4.2 CT Scanning

In patients who cannot undergo MRI scanning (e.g. pacemakers, extreme claustrophobia) computed tomography (CT) of the pituitary with 1mm slices should be performed, accepting the lower resolution compared with MRI. Wherever possible, MRI/CT should be reported by a Neuroradiologist with particular expertise in the assessment of sellar/parasellar disorders.

2.6.4.3 Nuclear medicine

Nuclear medicine modalities do not currently form part of routine clinical practice. However, modalities such as positron emission tomography (PET) or single-photon emission tomography

(SPECT) may be used to perform *in-vivo* characterisation of pituitary tissue and to differentiate PA from other neoplasms. ^{111}In-DTPA-octreotide scanning is of potential value in Cushing's Disease, acromegaly, thyrotropinoma (TSHoma), and NFPA(23), though other non-pituitary lesions (e.g. meningiomas) may also express somatostatin receptors and exhibit uptake of this isotope. The ^{11}C-labelled D2 receptor antagonists raclopride and N-methlyspiperone can also be used for positron emission tomography (PET) (±CT) imaging to assess functionality in prolactinomas(24). PET tracers such as ^{18}F-fluorodeoxyglucose and ^{11}C-methionine may also be employed to study rates of glucose metabolism and protein synthesis in pituitary tumours(24).

2.6.4.4 Interventional radiology

Inferior petrosal sinus sampling (IPSS) is usually performed in patients with ACTH-dependent Cushing's syndrome(25). IPSS helps to distinguish between a pituitary and ectopic source of ACTH secretion. Corticotroph PA are typically small and often cannot be localised with confidence even with high quality MRI. In addition, pituitary 'incidentalomas' are common in the general population (see above) and may erroneously be assumed to be the source of ACTH excess. Hence, IPSS is useful as it typically provides a clear distinction between a central (pituitary) and peripheral (ectopic) origin: if the central to peripheral gradient of ACTH before and after injecting CRH are >2:1 and >3:1 respectively, then this is strongly suggestive of a pituitary source of ACTH(25). It has also been proposed that even in cases with no obvious baseline central to peripheral gradient, a peak stimulated central to peripheral gradient of >2 at 5 minutes post CRH is 97% sensitive and 100% specific in diagnosing pituitary dependent disease (26). IPSS may also aid lateralisation of a PA within the pituitary fossa in approximately two thirds of cases(25). As with MRI/CT, IPSS should be performed by a Radiologist with appropriate expertise, and it should be undertaken before commencing agents such as metyrapone or ketoconazole.

2.6.5 Ophthalmic assessment

Visual acuity and visual fields must be assessed formally (ideally through an Ophthalmic service) if imaging reveals suprasellar extension or if there is clinical evidence of visual impairment. Assessment for other cranial nerve deficits [especially III, IV, VI] should also be performed if there is clinical suspicion of neuropathy and/or if imaging reveals parasellar extension into the cavernous sinuses.

2.6.6 Histopathology

Various histopathological classification systems have been proposed for PA(27). Historically, this was based on histochemical staining, which divides PA into acidophilic, basophilic and chromophobe adenomas. However, this has limited value in routine clinical practice. Immunohistochemical profiling primarily classifies PA according to secretory granule content. In addition, examining for immunoreactivity for certain transcription factors and keratins can provide

useful additional information in some cases. Among these the Ki-67 labelling index (detected by MIB-1) is the best studied and most widely used. Other proliferative indices and cell cycle markers have been proposed to assess the aggressiveness of PA and their potential for recurrence, but are not routinely employed in most centres. Similarly, ultrastructural classification based on electron microscopic findings can be helpful, but the availability of this technique limits its use. Ideally, histopathological findings should be reported by a Neuropathologist with particular expertise in sellar/parasellar disorders.

The system currently widely accepted is the World Health Organization (WHO) 2007 classification (Table 4) (28).

GH producing adenoma Densely granulated Sparsely granulated Mixed adenomas Mammosomatotroph adenoma Acidophil stem cell adenoma	**Gonadotroph producing adenoma**
PRL producing adenoma Densely granulated adenoma Sparsely granulated adenoma Acidophil stem cell adenoma	**Unusual plurihormonal adenoma** Silent subtype 3 adenoma
TSH producing adenoma	**Null cell adenoma** Hormone immunonegative adenoma Oncocytoma
ACTH producing adenoma Silent ACTH cell adenoma Subtype 1 – densely granulated Subtype 2 – sparsely granulated	**Others** Carcinoma Atypical adenoma

Table 4. WHO classification of pituitary tumours.

2.7 Treatment

The optimal choice of treatment for a pituitary tumour in any given patient is dependent on a number of factors including: mode of presentation, size of the tumour, functionality, compressive

symptoms, new diagnosis/recurrence, previous treatment and patient preference. Current therapeutic modalities include surgery, radiotherapy, medical treatment, chemotherapy (rarely), and 'watchful waiting' (with clinical, ophthalmic and radiological surveillance).

2.7.1 Prolactinomas

Microprolactinomas are almost always treated with oral dopamine agonist therapy and do not routinely require discussion at the MDT. Treatment is titrated to restore gonadal function and control other symptoms, although restoration of a completely normal prolactin level is not always necessary. Echocardiography is currently recommended at baseline and annually thereafter (or sooner if symptoms of cardiac valvular insufficiency develop during treatment) in patients receiving ergot-derived agents (e.g. bromocriptine, cabergoline), although there is considerable debate regarding the need for this in patients on low dose therapy (e.g. cabergoline total dose $\leq$2mg/week). Screening for other fibrotic disorders [e.g. pulmonary function tests (pleural/pulmonary fibrosis); erythrocyte sedimentation rate, renal ultrasound/CT/PET-CT (retroperitoneal fibrosis)] is generally reserved for those subjects receiving higher dosages/long-term therapy (most commonly patients with macroprolactinomas), or if clinical features develop during treatment with an ergot-derived agent. An attempt to withdraw dopamine agonist therapy is usually made every two years or at the natural menopause. Repeat imaging is not always required, although many patients find it reassuring to undergo one follow-up scan (typically 4-6 months after starting therapy). Further imaging should also be considered in cases where it is difficult to distinguish a prolactinoma from a small NFPA with 'stalk disconnection syndrome'.

Macroprolactinomas also frequently respond to medical treatment, but should always be discussed at the pituitary MDT to allow consideration of other treatment modalities. Scanning is usually repeated at 8-12 weeks post treatment initiation, and then at 12, and 24 months or as determined by MDT discussion.

2.7.2 Acromegaly

For GH-secreting tumours causing compressive symptoms/signs, surgery remains the preferred first line definitive treatment option. However, SRL therapy also affords control of tumour growth and hormone hypersecretion in a substantial proportion of patients and may be used as an adjunct to surgery and/or radiotherapy, or as primary medical therapy in selected cases(29). There is also evidence that presurgical treatment with both Lanreotide Autogel® and Sandostatin LAR® may improve surgical outcomes in some patients. A smaller number of subjects with acromegaly may also respond to dopamine agonists, and pegvisomant (a GH receptor antagonist) is licensed for use in those with persistent active disease despite surgery, radiotherapy and other medical therapy.

2.7.3 Cushing's disease

For ACTH-secreting tumours, metyrapone and/or ketoconazole can help to control/normalise cortisol levels. These are frequently administered to patients with a high cortisol burden for at least 6 weeks to aid medical optimisation preoperatively. They are also appropriately used following non-curative surgery while awaiting the benefits of radiotherapy and/or bilateral adrenalectomy.

2.7.4 Thyrotropinomas

These are rare tumours for which less data are available. Tumours causing compressive symptoms/signs should be offered surgery, though they may also respond to SRL therapy, radiotherapy or radiosurgery.

2.7.5 Surgery

For GH-, ACTH- and TSH-secreting PA and all NFPA causing compressive symptoms/signs surgery remains the preferred first-line 'definitive' treatment option in most centres. Surgery also has a key role to play in some patients with prolactinomas (e.g. intolerance of/refractory to dopamine agonists). Medical pre-treatment may be indicated in some patients as outlined above. There are a number of different surgical approaches that can be used to resect/debulk pituitary tumours including: transsphenoidal (most commonly performed transnasal/transseptal with or without endoscopic assistance) and transcranial (e.g. subfrontal, pterional, transcallosal). The decision to offer surgery, and choice of approach, should be made following careful discussion between the members of the pituitary MDT, taking in to account those individual factors highlighted above, and patient preference.

Pituitary surgery should take place in a unit with neurocritical care facilities, and senior endocrine expertise should be available on a daily basis to facilitate the peri-operative management of 'salt and water balance' and pituitary replacement therapy.

24/7 expert neurosurgical and endocrine cover should also be available to deal with pituitary emergencies, including apoplexy. UK guidelines for the management of pituitary apoplexy have recently been published (18) , and it is anticipated that these recommendations will be adopted by the AngCN pituitary MDT/SSG.

2.7.6 Radiotherapy

Radiotherapy is most often employed as an adjunct to medical or surgical therapy. Fractionated external beam radiation therapy reduces excessive hormone production and can prevent further growth/regrowth of residual tumour(30). Alternative modalities (e.g. Gamma Knife® or linear accelerator stereotactic radiosurgery) may have a role to play in a small number of cases(31).

There is often a delay before the benefits of radiotherapy are observed, especially with respect to control of hormone hypersecretion, and hence patients typically need to continue suppressive medical therapy for a variable period of time following treatment. Radiotherapy also carries with it a risk of developing/evolving more widespread hypopituitarism, which can present several years down the line. In a small number of cases, second tumours (e.g. meningioma) may occur within the radiation field, and an increased rate of cerebrovascular disease has also been reported in some studies(32). Pituitary radiotherapy should be supervised by a Radiation Oncologist with appropriate expertise in treating sellar/parasellar tumours, although since radiotherapy is usually delivered over at least 25 visits, this should be delivered close to home wherever possible.

2.7.7 Chemotherapy

Chemotherapy is only rarely used in the management of pituitary tumours. For aggressive/malignant pituitary tumours traditional chemotherapy regimens (e.g. cisplatinum, etoposide, 5-fluorouracil) have been used(6, 33-35). More recently temozolomide has been shown to be effective in controlling aggressive pituitary tumours including metastatic disease(36, 37).

2.7.8 Watchful monitoring

Watchful monitoring with periodic assessment of visual status and interval MRI/CT scanning may be appropriate for some cases, e.g. incidentally discovered NFPA without compressive features.

2.8 Follow-up

For most patients periodic reassessment of endocrine, ophthalmic and radiological appearances will be required, especially in those who have undergone surgical intervention and/or received radiotherapy. An example of a follow up regime suitable for a patient with a NFPA and intact pituitary function post surgery is outlined in Table 5.

Timepoint post-surgery	Investigations
1 week	U+E, osmolalities
6 weeks	Baseline +/- dynamic pituitary function testing Formal visual field testing
3 months	Consider early postoperative MRI
5-6 months	Baseline +/- dynamic pituitary function testing 1st postoperative MRI if not performed at 3 months
12 months	Baseline pituitary function testing (+/- dynamic testing following

Timepoint post-surgery	Investigations
	radiotherapy, or of functional tumours to reassess for 'ongoing cure') Formal visual field testing
15-18months	2nd postoperative MRI (i.e. 12 months after 1st postoperative scan)
18 months	Baseline pituitary function testing
2 years	Baseline +/- dynamic pituitary function testing (as above) Formal visual field testing
3 years	Baseline +/- dynamic pituitary function testing (as above) Formal visual field testing
3–3.5 years	3rd postoperative MRI (i.e. 24 months after 2nd postoperative scan)
4 years	Baseline +/- dynamic pituitary function testing (as above) Formal visual field testing
5 years	Baseline +/- dynamic pituitary function testing (as above) Formal visual field testing
5–5.5 years	4th postoperative MRI (i.e. 24 months after 3rd postoperative scan)

Table 5. Example of a 'Follow up' algorithm following pituitary surgery.

Endocrine re-evaluation is likely to involve a similar combination of tests to those outlined above (section 2.6.3), and should be tailored to the individual. For example, an annual baseline reassessment is indicated in all patients whatever their pituitary status, and other measures may be used to help gauge the adequacy of pituitary replacement therapy periodically (e.g. hydrocortisone day profile). However, dynamic pituitary function testing is also required on an ongoing basis (e.g. on alternate years) in patients apparently eupituitary following radiotherapy.

All patients should undergo repeat ophthalmological assessment post-surgery, and periodically (e.g. annually) thereafter (which may be undertaken via their optician) as dictated by their initial presentation and extent of residual tumour.

The timing of follow-up MRI/CT scans should be determined by the local pituitary SMDT on a case by case basis. As a general rule of thumb the first postoperative scan is typically carried out between 3 to 6 months (early post-operative scans may be difficult to interpret due to post-operative inflammatory changes). Thereafter, it is reasonable to perform 'routine' surveillance scans at 12, 24 and 24 month intervals (i.e. 1, 3 and 5 years after the first post-operative scan). The interval

between scans may then be increased (eg to 5 yearly), and the decision to continue long-term radiological surveillance should be made on an individual case basis.

Patients with small functioning tumours that are completely excised, with biochemical remission demonstrable post-operatively and no evidence of residual tumour on follow-up MRI, may be recommended for combination clinical and biochemical surveillance with repeat imaging only in the event of clinical concern.

Conversely, earlier imaging is indicated if there is clinical/ophthalmic concern regarding possible tumour recurrence, interval growth or atypical tumours (e.g. craniopharyngiomas: see section 2.5.3) If a patient receives radiotherapy, then a return to a scanning interval of 3-6 months post-treatment, followed by further scans at years 1, 3 and 5 (as outlined above) is advised, but again with tailoring to the individual case.

2.9 Pregnancy

Significant enlargement of macroprolactinomas during pregnancy may occur due to the physiological hormonal changes of pregnancy and withdrawal of dopamine agonist therapy. Such enlargement is rare in microadenomas. For intrasellar tumours it is reasonable to discontinue dopamine agonist therapy once pregnancy is confirmed. Both bromocriptine and cabergoline are considered safe in early gestation, although the latter is not licensed for use in pregnancy and therefore the patient should be counselled accordingly. For tumours with significant suprasellar extension consideration should be given to continuing bromocriptine (or cabergoline if agreed with the patient) throughout pregnancy. Patients should be reviewed each trimester for symptoms of enlargement (i.e. headaches or visual disturbance), and suprasellar tumours should be monitored with formal visual field testing. Intervention is required in approximately 30% of patients with macroadenomas (38). Reintroduction of a dopamine agonist is the usual first line therapy. Transsphenoidal surgery or delivery, depending on the gestational age are second line options.

Other pituitary tumour types are likely to be encountered in pregnancy only rarely. Maternal hypercortisolaemia is associated with poor outcome, and definitive transsphenoidal surgery is recommended, usually in the second trimester. Medical therapy with metyrapone or ketoconazole should only be considered second line (39). Growth hormone secreting tumours have a low propensity to enlarge during pregnancy, but should be monitored clinically and with visual field testing as appropriate. There is limited data on the safety of somatostatin analogues in pregnancy, and therefore these should usually be discontinued if conception is being considered. Women with acromegaly are at increased risk of gestational diabetes and hypertension during pregnancy, and should be monitored accordingly (40). NFPA are unlikely to enlarge during pregnancy, but

occasionally the lactotroph hyperplasia of adjacent normal pituitary tissue is sufficient to cause optic chiasmal compression. Bromocriptine may be effective in this situation (41). TSH - secreting adenomas have been successfully managed with somatostatin analogues for tumour size and the associated hyperthyroidism (42).

3.0 Pituitary SMDT referral criteria

All patients with sellar and parasellar disorders should be considered for discussion at the pituitary MDT; however, the following patients in particular should be referred for review:

- All new functional and non-functional pituitary macroadenomas
- All new functional microadenomas apart from prolactinomas
- All craniopharyngiomas (including during long term surveillance follow up)
- All new sellar-related lesions with suprasellar and/or parasellar extension(s) – including those detected incidentally
- Previously treated (surgery/radiotherapy or both) functional and non-functional macroadenomas where there is a need for ongoing advice regarding possible further treatment and/or radiological surveillance intervals, especially those within 5 years of undergoing surgery and/or radiotherapy.
- All macroprolactinomas (including those being considered for medical therapy) at presentation, and again at 3-6 months following commencement of dopamine agonist treatment. These patients should be discussed again whenever a change in management strategy is necessary, e.g. patients intolerant of medical therapy, or patients with a poor response to, or high dose requirement of, medical therapy to consider radiotherapy or surgery.
- All suspected/confirmed cases of pituitary carcinoma
- Pregnancy with PA (aside from microprolactinoma)
- Patients with a microprolactinoma desiring surgery
- Pituitary apoplexy (especially with neurological symptoms and signs or where there is other clinical concern)
- Malignancy elsewhere with an incidental pituitary lesion

Patients that do not routinely require discussion at the SMDT include the following:

- Incidental non-functional microadenomas (apart from indications listed above)
- Microprolactinomas (apart from indications listed above)

If any patient needs discussion before the next SMDT meeting, the relevant core members should be contacted immediately, and the patient discussed retrospectively at the next SMDT.

4.0 Pathology Guidelines

See AngCN Document:
AngCN-SSG-15 – Pathology Guidelines for Brain and CNS – for cuurent version see AngCn website
http://www.angliacancernetwork.nhs.uk/module_dm.php?menu_id=694&parent_id=44&level=3

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