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SPECIAL ARTICLE

Recommendations on the pathological report of pituitary tumors. A consensus of experts of the Spanish Society of Endocrinology and Nutrition and the Spanish Society of Pathology☆

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Abstract Pituitary neuroendocrine tumors (PitNETs) constitute, together with other tumors of the sellar region, 15-25% of intracranial neoplasms. In 2017, the World Health Organization proposed a new classification of PitNETs. The main innovation with respect to the 2004 classification was the recommendation to include in the immunohistochemical evaluation of PitNETs the determination of the transcription factors of the 3 pituitary cell lineages: Pit-1, Tpit and SF-1. Additionally, other clinicopathological classifications with a predictive capacity of tumor behavior during follow-up were proposed. Given these changes, it is appropriate to adapt the knowledge generated during the last 15 years to the daily practice of the treatment and

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monitoring of PitNETs at the Centers of Excellence in Pituitary Pathology. This document includes the positioning of the Spanish Society of Endocrinology and Nutrition (SEEN) and the Spanish Society of Pathology (SEAP) on the classification and denomination of the PitNETs and the information that the pathologist should provide to the clinician to facilitate the treatment and monitoring of these tumors.

PALABRAS CLAVE
Tumores neuroendocrinos;
Anatomía patológica;
Inmunohistoquímica;
Recomendaciones de expertos

Recomendaciones sobre el diagnóstico e informe anatomopatológico de los tumores neuroendocrinos hipofisarios. Consenso de expertos de la Sociedad Española de Endocrinologia y Nutrición y de la Sociedad Española de Anatomía Patológica

Resumen Los tumores neuroendocrinos hipofisarios (TNEH) constituyen, junto con otros tumores de la región selar, un 15-25% de las neoplasias intracraneales. En 2017, la Organización Mundial de la Salud propuso una nueva clasificación de los TNEH. La principal innovación respecto a la clasificación del 2004 fue la recomendación de incluir en la evaluación inmunohistoquímica de los TNEH la determinación de los factores de transcripción de las 3 líneas celulares hipofisarias: Pit-1, Tpit y SF-1. Adicionalmente, se han propuesto otras clasificaciones clínico-patológicas con capacidad predictora del comportamiento tumoral durante el seguimiento. Ante estos cambios, procede adaptar el conocimiento generado durante los últimos 15 años a la práctica diaria del tratamiento y seguimiento de los TNEH en los centros de excelencia de patología hipofisaria. El presente documento recoge el posicionamiento de la Sociedad Española de Endocrinología y Nutrición (SEEN) y la Sociedad Española de Anatomía Patológica (SEAP) sobre la clasificación de los TNEH y la información que el patólogo debe proporcionar al clínico para facilitar el tratamiento y seguimiento de estos tumores.

Introduction

Pituitary neuroendocrine tumors (PitNETs),[1] together with other sellar region tumors, account for 15%–25% of intracranial neoplasms.[1–5] Their incidence has gradually increased in parallel to the use of increasingly sensitive brain and cranial imaging techniques.[6,7] Although adenohypophyseal tumors account for 85%–90% of all tumors, there are other lesions in the sellar region, such as mesenchymal, meningeal, or neural neoplasms, metastases of multiple origins, and cysts or inflammatory processes.[2–5]

PitNETs have traditionally been called adenomas because of their usual indolent behavior as compared to other neoplasms and neuroendocrine tumors in other locations. Recently, the International Pituitary Pathology Club proposed, at its fourteenth meeting held in Annecy in November 2016, replacement of the term adenoma by pituitary neuroendocrine tumor (PitNET)1. According to the authors, this term would better reflect the similarities between adenohypophyseal tumors and neuroendocrine tumors in other organs and the aggressive behavior of some of the former. However, this proposal has recently been controversial.[8,9]

The terminological debate also extends to the widespread use of the generic acronym NFPAs (non-functioning pituitary adenomas). All hormonally active PitNET subtypes have silent homologues that have been grouped under the acronym NFPA. The terms silent pituitary adenoma or silent PitNET describe adenohypophyseal tumors that express one or more adenohypophyseal hormones or their transcription factors in immunohistochemistry (IHC) but do not secrete hormones in clinically relevant levels.[5,10,11] However, both terms have been used indistinctly in literature to refer to the same type of tumor.

The recent 2017 WHO classification groups PitNETs into the three cell lines of the adenohypophysis from which they derive using measurement by IHC of the corresponding pituitary transcription factors (PTFs). This grouping allows for a different approach to the pathological diagnosis of PitNETs. Specifically, it has allowed for a drastic reduction in the proportion of null tumours and for a more precise classification of plurihormonal tumors.[10,12] In addition, it has been proposed that the pathology report also includes clinical data (functioning/silent tumor; presence and extent of radiographic invasion) and proliferative activity data (MIB1-LI/Ki-67, number of mitosis, and p53). The final objective was to design a clinical-pathological classification of PitNETs with prognostic capacity of their behavior.[13–15] This proposal has been supported by the European Pituitary Pathology Group.[16] However, not all pathologists agree, because they think that this report would only be available to centers of excellence that had neuropathologists specialized in pituitary disease. In contrast, they argue that it is sufficient that the pathology report includes gross data and results of hematoxylin-eosin staining, adenohypophyseal hormone immunostaining, and MIB1-LI/Ki-67.[17]

In either case, the pathology report is essential for adequate planning of treatment and follow-up of PitNETs. Pathologists should therefore be part of the multidisciplinary clinical teams caring for patients with pituitary tumor disease.

The recent changes introduced by the WHO classification in 2017[2] and the terminological controversies regarding neuroendocrine tumors and the contents of the pathology report warrant this document. The objective is to establish the positioning of the Neuroendocrinology Knowledge Area of the Spanish Society of Endocrinology and Nutrition (SEEN) and the Spanish Society of Pathology (SEAP) on the classification and naming of PitNETs and the information that the pathologist must provide to the clinician (endocrinologist/neurosurgeon) to facilitate the treatment and follow-up of these tumors.

The new 2017 classification of neuroendocrine pituitary tumors: What are its contributions?

The fourth edition of the WHO Classification of Tumors of Endocrine Organs[2] was published in 2017 to serve as a reference for all specialists involved in their diagnosis and treatment. This edition has taken into account the expression of PTFs in pituitary cell lines, together with the structural characteristics and genetic changes of PitNETs (Table 1). The main changes include:

a) It is recommended to measure the PTFs of the three pituitary cell lines: the pituitary-specific transcription factor 1 (Pit-1), the transcription factor T-PIT, and the steroidogenic factor 1 (SF-1).
b) The term atypical adenoma, proposed in the 2004 classification, was removed. In contrast, high risk subtypes, characterized by a greater capacity to invade, relapse, and metastasize than the other PitNETs, are identified.
c) The recommendation to determine the MIB1-LI/Ki-67 index as a proliferative marker is maintained, and measurement of p53 is relegated to tumors with Ki-67 $\geq$ 3%.
d) Pituitary blastoma is included as a new entity.

Additional IHC study of adenohypophyseal hormones and low molecular weight cytokeratins allows for identification of PitNET types with variants related to structural and behavior-predicting aspects.

Classification also allows for identifying silent homologous variants of the different functioning subtypes and for significantly reducing the proportion of truly null tumors.

Non-functioning neuroendocrine pituitary tumors

Since the proliferation of highly sensitive imaging techniques, non-functioning PitNETs have been the most frequently diagnosed pituitary neuroendocrine tumors in both surgical and non-surgical series.[18] PitNETs not associated with a recognizable clinical hormonal syndrome have historically been grouped under the acronym NFPAs. NFPAs are most commonly macroadenomas and may cause symptoms related to a mass effect (headache or neuroophthalmological changes), partial or total hypopituitarism, and hyperprolactinemia, or be incidentally discovered on a brain MRI. When the cell line from which the tumor is derived is identified after surgery and the tumor is not associated to a systemic endocrine syndrome, the tumor is said to be *silent*.[5,10,11] Thus, after surgery, the term NFPA should be replaced by the corresponding tumor cell type accompanied by the adjective *silent*; for example, silent corticotroph PitNET, silent lactotroph, etc., to differentiate it from the respective functional variant. Approximately 10% of gonadotroph PitNETs are functioning.[19] The adjectives *silent* and *functioning* should therefore also be applied to this subtype of PitNETs. Null cell PitNETs, increasingly uncommon with advances in the accuracy of diagnostic techniques, should be labeled as such. The clinical spectrum of PitNETs shows a continuum of hormone secretion between functioning and totally silent tumors.[20] The term *totally silent* has been used for pituitary tumors of a given subtype where circulating levels of the corresponding hormone are rigorously normal.[21] The term *clinically silent* would refer to tumors that have somewhat elevated circulating hormone levels autonomously, but without expressing the corresponding clinical syndrome.[21] In addition, the functional status of a PitNET may change during follow-up, more frequently in the case of tumors of corticotroph lineage.[22–24]

This terminological heterogeneity has undoubtedly conditioned the results and conclusions of many published series. Increasingly accurate pathological typing of PitNETs has identified the cell identity of more than 95% of pituitary tumors and decreased the proportion of null tumors to less than 3%.[10,25,26] Thus, due to the different behavior of tumors derived from different pituitary cells, the term NFPAs should be used for PitNETs with no associated endocrine syndrome only before surgery, and should be subsequently replaced by the corresponding silent subtype.

Aggressive tumors

The definition of *aggressive tumor* is controversial and has also been used heterogeneously in the literature. THE 2004 WHO classification introduced the concept of *atypical adenoma* for adenomas with: (1) a mitotic index >10 mitoses per field; (2) a Ki-67 proliferation index $\geq$3%; and (3) strong nuclear staining for p53. The 2017 WHO classification deleted the term *atypical adenoma*. Instead, it recognized high-risk adenoma subtypes with a poorer prognosis during follow-up: lactotroph adenomas in males, silent corticotroph and Crooke cell adenomas, sparsely granulated somatotroph adenomas, and silent Pit-1 plurihormonal tumors. Pit-1 plurihormonal tumors replace the previously called subtype 3, a tumor characterized by its occurrence in young patients and with a higher rate of persistent or recurrent disease during follow-up.[27] In addition, immunostaining of Ki-67 is still recommended as a proliferation criterion, and immunostaining of p53 only when it Ki-67 is $\geq$3%.

The European Society of Endocrinology[28] recently defined aggressive pituitary tumor as ''large tumors with radiographic invasion of adjacent structures and unusual growth, or with recurrence despite optimal treatment.'' However, the concepts of invasion and aggressiveness are often confused, since an invasive tumor may not be aggressive while all aggressive tumors are invasive. Thus, because of the

Table 1 Classification of pituitary neuroendocrine tumors.

Type of adenoma or PitNET	Morphological variant	Pituitary hormones and other immunomarkers	PTFs and other cofactors
Somatotroph adenoma	Densely granulated	GH ± PRL ± subunit α Perinuclear or diffuse cytokeratin pattern	PIT-1
	Sparsely granulated	GH ± PRL, dot-like pattern of cytokeratins	PIT-1
	Mammosomatotroph	GH + PRL (in same cells) ± subunit α	PIT-1, ERα
	Mixed somatotroph-lactotroph	GH + PRL (in different cells) ± subunit α	PIT-1, ERα
Lactotroph adenoma	Densely granulated	Diffuse PRL	PIT-1, ERα
	Sparsely granulated	Perinuclear PRL	PIT-1, ERα
	Acidophilic stem cell	PRL, GH (focal and variable) Dot-like pattern of cytokeratins	PIT-1, ERα
Thyrotroph adenoma		β-TSH, subunit α	PIT1, GATA2
Corticotroph adenoma	Densely granulated[a]	ACTH Diffuse pattern of cytokeratins	T-PIT
	Sparsely granulated	ACTH Diffuse pattern of cytokeratins	T-PIT
	Crooke cell	ACTH	T-PIT
Gonadotroph adenoma		β-FSH, β-LH ± subunit α	SF-1, CAT2, ERα
Null cell adenomas		None	None
Plurihormonal adenoma	PIT-1 plurihormonal adenoma	GH, PRL, β-TSH ± subunit α	PIT-1
	Adenomas with unusual combinations	Miscellaneous combinations: ACTH/GH, ACTH/PRL	N/A

Modified from the WHO classification of pituitary gland adenomas.[2] PTFs: Pituitary transcription factors.

discrepancy of clinical and pathological criteria, these concepts should be differentiated: (1) *invasion:* radiographic or anatomical invasion of the sinuses adjacent to the sella turcica, regardless of Ki-67 expression; (2) *proliferation:* MIB1-LI/Ki-67 immunostaining $\geq$3%, regardless of the presence or absence of invasion; and (3) *aggressiveness*: invasive tumor that relapses or grows during follow-up despite adequate treatment, regardless of proliferation markers.

Null cell tumor or immunonegative tumor?

Null cell tumor is an adenohypophyseal cell tumor that does not show specific cell differentiation on IHC of adenohypophyseal hormones or PTFs. The terms *adenoma immunonegative for pituitary hormones* or *adenoma immunonegative for PTFs* have therefore been proposed as synonyms.[29] Microscopically, null cell tumors consist of chromophobic or somewhat acidophilic cells, arranged in a leaf-shaped pattern. They differ from gonadotropinomas in that papillary or pseudopapillary growth patterns are less common. Their prevalence has changed greatly in recent series, following use of antibodies more specific to pituitary hormones,[15] IHC study of PTFs,[10] and molecular gene expression studies of pituitary hormones[30,31] and their PTFs.[26] Their current prevalence is less than 3% in all mentioned series, when prevalence rates ranging from 5% and 30% of surgical series had initially been reported.[32,33]

With the new procedures, most tumors initially considered as null tumors are reclassified as gonadotropinomas (most of them express SF-1) or, less commonly, as silent corticotropinomas.[34,35] Since truly null tumors and silent corticotropinomas may behave more aggressively than gonadotropinomas,[36,37] adequate identification is very important. Because of immunonegativity for pituitary hormones and PTFs, diagnosis is exclusionary, and the current recommendation is to call them immunonegative tumors rather than null tumors.

Pathological study of pituitary neuroendocrine tumors

Diagnostic work-up of pituitary disease should be performed by a pathologist and, if possible, depending on the characteristics of the center, by a pathologist or neuropathologist with proven experience in pituitary disease. It is recommended that part of the tumor tissue is reserved for cryopreservation and storage in biobanks, together with peripheral blood samples to complete somatic studies with germline studies. Creation of collections of neuroendocrine tumors in the respective biobanks that can interact in network is also advised.

Clinical information that the pathologist should know before the study

Pathological diagnosis is made in a clinical setting, and it is therefore essential that the pathologist receives the necessary background information. In agreement with the European Pituitary Pathology Group,[16] the authors recommend that the pathologist has access to the information included in Table 2.

Sample collection and shipping conditions

It is recommended that biological material is sent fresh and without fixative immediately after collection to prevent tissue ischemia.[3,4,38] Ideally, the material will be sent in a gauze moistened with saline to prevent its disintegration in a container filled with solution. All tissue obtained should be submitted to the pathology department, and manipulation in the surgical area should be avoided as much as possible. Before fixation, the pathologist will send part of the sample to the corresponding biobank for cryopreservation.

Gross analysis and processing of tissue

Gross analysis should describe the number of fragments and their approximate volume. The pathologist is responsible for selecting the tissue to be used for special techniques or for biobanks, always prioritizing the diagnostic needs. Microscopic control of the sample before freezing is recommended, and can be done quickly with a cytological sample by crushing a small fragment.[38]

When an intraoperative diagnosis is required, and in order to prevent tissue loss and appearance of artifacts that occur in frozen sections, cytology by smear or crushing of a small fragment is recommended.[3,4,39,40]

Microscopic study

The tumour tissue for the diagnostic study will be fixed in neutral buffered formalin (for 6–48 h). Mercury- or picric acid-based (Bouin) fixatives should not be used.[3,4,16,38,40] Initial evaluation is performed with hematoxylin-eosin staining to confirm that it is a PitNET.[2–4,16,34,38,39] The staining type, cell characteristics (degree of pleomorphism), architecture, extent of fibrosis, necrosis, signs of bleeding or any other morphological parameter of interest will be determined. Presence of normal pituitary tissue will be reported if it is part of the biological material submitted. If there is any doubt that the biological material if from the normal pituitary gland rather than the tumor, a reticulin stain will be performed. This technique is especially recommended for Cushing's disease if no tumor has been identified on MRI. The number of mitoses in 10 fields (40$\times$) will be quantified.[2,16,39]

Immunohistochemical study

The immunohistochemical study will allow for characterizing the tumor and for determining variables of response to the drug treatment of prognostic interest.[2,16,34,41,42] It should be noted that there are no studies comparing the diagnostic performance depending on the antibodies used, the visualization system, the quantification or the cut-off points that define positivity. Thus, each laboratory must define and validate its procedures. However, the studies on the agreement and validation of IHC and the molecular study recently reported[30,31,43] suggest that positive values in IHC < 5% should be interpreted with caution when a given

Table 2 Information to be provided by the clinician (endocrinologist/neurosurgeon) to the pathologist together with the tissue sample to be analyzed.

Type of sample	• Intraoperative biopsy • Final tumor tissue • Normal pituitary gland • Other
Suspected diagnosis	• Endocrine clinical syndrome • Non-functioning
Family history	• Multiple endocrine neoplasia, isolated familial pituitary adenoma, Carney syndrome, pheochromocytoma/paraganglioma
Tumor size	• Largest diameter in millimeters
Surgical procedure performed	• Transsphenoidal, microscopic, transcranial
Radiographic characteristics	• Invasion of cavernous sinuses, sphenoidal sinuses, or clivus • T2 intensity
Degree of excision	• Total, partial, biopsy
Prior treatment	• Surgery (repeat) • Radiotherapy (conventional, stereotactic, radiosurgery) • Pharmacological: 1st and 2nd generation somatostatin analogues, dopamine agonists, pegvisomant, ketoconazole

tumor subtype is classified. Luckily, measurement by IHC or molecular techniques of PTFs will allow for adequate typing of these doubtful cases.

Immunostaining of pituitary hormones and pituitary transcription factors in pituitary cell lines

The European Pituitary Pathology Group[16] recently proposed stepwise stratification of immunohistochemical studies (Table 3).

However, at centers where PTFs may be routinely measured, a different diagnostic sequence is proposed, as shown in Fig. 1. This scheme would be more efficient for accurate identification of most PitNETs and would result in substantial antibody and time savings. Identification or plurihormonal tumors will not be as accurate using this approach, but they account for less than 1% of all PitNETs25.

Quantification by cytokeratin immunohistochemistry

Measurement of expression of low molecular weight cytokeratins, particularly cytokeratins 8 and 18, usually identified using the antibody CAM5.2 (CK8 and CK7), is useful for consistent identification of some variants of the PitNET subtypes, particularly the two main somatotropinoma subtypes. A diffuse perinuclear pattern of cytokeratins is diagnostic of densely granular somatotropinoma, while a dot-like pattern with a proportion of fibrous bodies >70% identifies sparsely granular somatotropinomas. Differentiation and inclusion of these two patterns in the pathology report is relevant for clinicians, because densely granular somatotropinomas have a better response to first-generation somatostatin analogues.[44] An abundant cytoplasmic expression pattern is also associated with corticotroph PitNETs. However, most adenomas negative for cytokeratins are gonadotroph adenomas,[16,34,39] and cytokeratin measurement would not be indicated in this subtype.

Assessment of proliferation: MIB1-LI/Ki-67 index

It is important that cell proliferation is estimated by immunohistochemical quantification of the MIB1-LI/Ki-67 staining index because this has been considered as a possible prognostic factor in PitNETs[2,16,42] (Table 3). Quantification with Ki-67 will be performed in two of the areas of the preparation with the greatest number of hot spots, considering between 500 and 1000 cells,[16] and will be expressed as a percentage over the total number of tumor cells. Unlike for other neuroendocrine tumors, no cut-off point that accurately predicts aggressive behavior of the tumor has been established in PitNETs[2,16]. It is accepted that most aggressive tumors have a Ki-67 $\geq$ 3% [28], and if Ki-67 is greater than 10%, the possibility of sellar metastasis or a pituitary carcinoma should be considered[45,46].

Other prognostic markers: number of mitoses and p53-immunostaining intensity

Quantification of the number of mitoses in PitNETs is not as important as for grading neuroendocrine tumors of the gastrointestinal tract. The result is expressed per square millimeter, which is equivalent to 5 high-power fields (40×), and presence of two mitoses per 10 high-power fields is relevant.[16,42] p53 positivity in tumor tissue suggests mutations or inactivation of the suppressor gene *TP53* and is considered a marker of aggressive behavior in many solid tumors.[47] Its prognostic significance in PitNETs is however limited.[2] Measurement of p53 is therefore only recommended in tumors with a Ki-67 index $\geq$3%, which saves costs and facilitates a homogeneous diagnostic strategy applicable to all hospitals in the country.

Other immunohistochemical measurements

In null tumors, immunostaining of chromogranin A (CgA) and synaptophysin may be helpful to certify the neuroendocrine origin of the lesion and differentiate it from other tumors in the sellar region.[48]

While several publications suggest that expression of the pituitary tumor transforming gene (PTTG) would help predict aggressiveness of PitNETs, this has not been supported by large series.[13] Measurement of PTTG is therefore not advised. Study of somatostatin receptor expression may help

Table 3 Multilevel recommendations of the immunohistochemical study of pituitary neuroendocrine tumors according to the recommendations of the European Pituitary Pathology Group[16]

LEVEL 1 Hormones Cytokeratins Proliferation markers	PRL/GH/TSH	ACTH	FSH/LH	LMWK[a]	MIB1/Ki-67
LEVEL 2 Pituitary transcription factors	PIT-1		T-PIT		SF-1
LEVEL 3 For selected cases only (see main text)	CgA[b]		SSTR, E-cadherin		P53

ACTH: corticotropic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; LMWK: low molecular weight cytokeratins; MIB1/Ki-67: MIB1 proliferation index; PIT1: pituitary-specific transcription factor 1; PRL: prolactin; SF-1: steroidogenic factor 1; SSTR: somatostatin receptors; TPIT: T-box transcription factor; TSH: thyroid-stimulating hormone.

[a] Study indicated for somatotroph and corticotroph tumors.

[b] Chromogranin (CgA) measurement is mandatory for all immunonegative or poorly positive tumors.

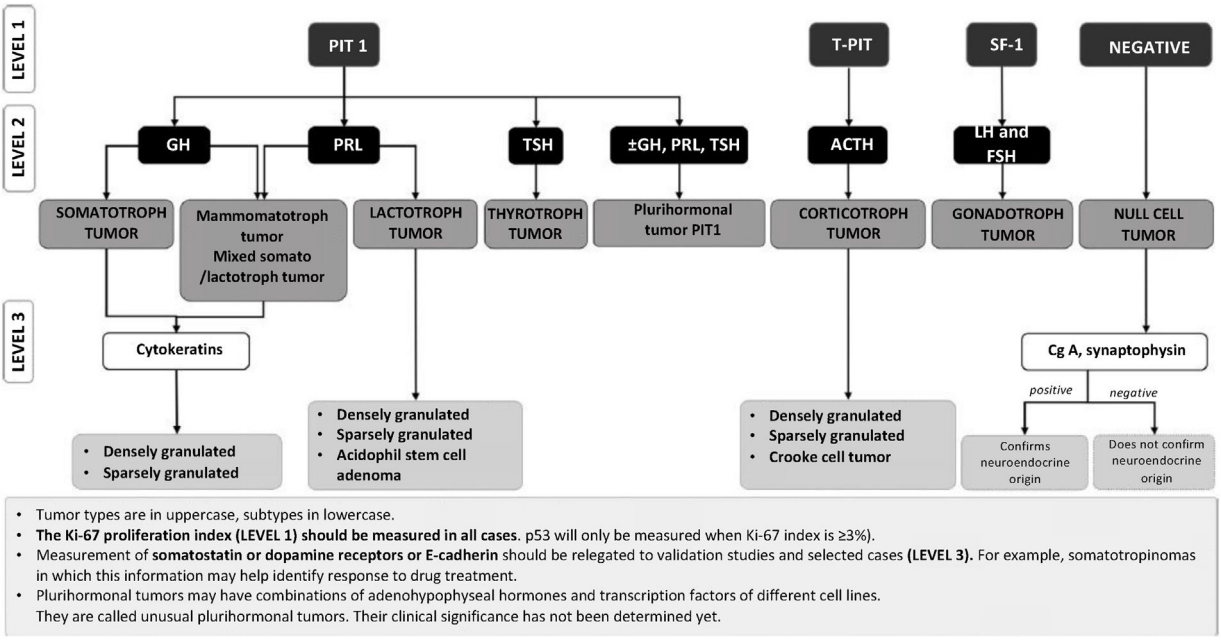

Figure 1 Proposed algorithm for diagnosing PitNET subtypes based on measurement of pituitary PTFs in a first step.
PIT-1: pituitary-specific transcription factor 1; T-PIT: T-box transcription factor; SF-1: steroidogenic factor-1. ACTH: corticotropic hormone; GH: growth hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin; TSH: thyroid-stimulating hormone. Cg-A: chromogranin A.

predict the response of somatotropinomas and NFPAs to treatment with first- and second-generation somatostatin analogues.[49–51] In addition, recent studies have shown that measurement of E-cadherin allows for more accurate identification of the response to somatostatin analogues than SSTR expression.[42,43,52] However, treatment algorithms for acromegaly do not include yet routine IHC measurement of SSTR or E-cadherin in daily clinical practice. These substances are therefore only measured for the time being for research purposes or in duly justified specific cases.[2,16]

Methylguanine methyltransferase (MGMT), the DNA repair enzyme that attenuates the effect of temozolomide in the treatment of aggressive carcinomas and PitNETs, has been proposed as a marker of negative response to this drug. Recent data have not confirmed that MGMT expression, IHC, methylation of the MGMT promoter or proliferative index values with Ki-67 or p53 are predictors of response to temozolomide.[53] Moreover, there is no agreement on how to assess MGMT. Routine measurement of MGMT is therefore not currently warranted as a predictor of response.

Alternatives proposes to MGMT testing include evaluation of DNA repair proteins, particularly MSH6, whose expression has been associated with response to temozolomide.[54] Loss of nuclear immunoexpression of MSH6, and also of MSH2, has been associated with loss of efficacy of treatment with temozolomide. However, current data on the value of this drug are very scant.

Table 4 Proposed pathology analysis report for PitNETs.

Clinical and preoperative information				
Functioning adenoma ☐ Yes / ☐ No	**Preoperative treatment** ☐ Surgery ☐ Dopamine agonists ☐ Somatostatin analogues	☐ Pegvisomant ☐ Ketoconazole ☐ Antithyroid drugs	☐ Radiotherapy	**Relapse** ☐ Yes / ☐ No
Surgical procedure performed				
Preoperative MRI available? ☐ Yes / ☐ No		**Largest diameter in millimeters**		
Radiological invasion:	**Cavernous sinus** ☐ Yes ☐ No ☐ Unknown	**Sphenoidal sinus** ☐ Yes ☐ No ☐ Unknown	**Other bone** ☐ Yes ☐ No ☐ Unknown	
Macroscopic examination				
Size of specimen				
No. of fragments fixed in_____*(state fixative)*				
No. of fragments cryopreserved				
Histological examination				
Hematoxylin-eosin	**Cell type** ☐ Acidophilic ☐ Basophilic ☐ Chromophobic	**Pattern** ☐ Diffuse ☐ Trabecular ☐ Pseudopapillary ☐ Other_____	☐ Adenohypophysis ☐ Neurohypophysis	**Other characteristics** ☐ Oncocytic change ☐ Calcification ☐ Inflammation ☐ Other:
				☐ Necrosis ☐ Fibrosis
Reticulin stain Contains non-tumoral pituitary gland: ☐ Yes / ☐ No			**Crooke cells** ☐ In adenohypophysis	☐ Yes / ☐ No ☐ In adenoma
Mitotic cell count (no. per square millimeter. 40X magnification)				
Histological infiltration (if applicable)			**Dura** **Bone** **Respiratory mucosa**	☐ Yes / ☐ No ☐ Yes / ☐ No ☐ Yes / ☐ No
Immunohistochemistry (antibody panel, note clone reference)				
Hormones	GH____% PRL____%		TSH____% ACTH____%	LH____% FSH____%
Pattern of cytokeratins	☐ Diffuse cytoplasmic ☐ Dot-like pattern ☐ Membrane		☐ Perinuclear	☐ Negative
Proliferation markers	**MIB-1/Ki-67 Index**		% positive cells	
Pituitary transcription factors (include percentage if positive)	**PIT-1** ☐ positive____% ☐ negative		**T-PIT** ☐ positive____% ☐ negative	**SF-1** ☐ positive____% ☐ negative
Chromogranin A (CgA)			☐ positive / ☐negative	
p53 (if MIB1/Ki-67 index ≥3%)*				%
Other techniques				
Final diagnosis (WHO 2017)				
Morphological classification with/without evidence of proliferation (mitotic count and Ki-67 index)[2]				
Integrated diagnosis with grades 1a, 1b, 2a, 2b, 3 (Table 5) [13,14]				

*Optional and conditional on Ki-67 proliferation index.

The pathology report

As in other areas of pathology, use of standardized pathological report templates is recommended.[16,2,4,13,16,34,38,39,55,56] The report must contain clinical data, radiographic data, surgery data, and pathology data including those from microscopy and IHC of adenohypophyseal hormones and, if available, PTFs (Tables 4 and 5).

Future contributions of molecular biology to typing and prognosis of pituitary neuroendocrine tumors

The description of the IHC study has mentioned the current limitations of certain markers, such as PTTG, for predicting aggressiveness or those of somatostatin receptors (classical SSTR1-5, and truncated sst5TMD4) or E-cadherin for predict-

Table 5 Clinical-pathological classification of pituitary neuroendocrine tumors according to Trouillas et al., 2013.[9,14]

The classification is based on 3 characteristics:	
1. Tumor diameter as micro (<10 mm), macro (≥10 mm) or giant (≥40 mm) according to MRI study	
2. Type of tumor according to immunohistochemical study: GH, PRL, ACTH, FSH/LH, and TSH	
3. Tumor grade based on the following criteria:	
Invasion: defined as histological or radiographic (MRI) evidence of cavernous sinus or sphenoid invasion	
Proliferation: based on presence of at least 2 of the 3 criteria:	
• *Ki-67:* >1% (Bouin-Hollande fixative) or ≥3% (formalin fixative)	
• *Mitoses: n* >2/10 high-power fields	
• *P53:* positive (>10 strongly positive nuclei/10 high-power fields)	
Grades of tumor behavior established according to previous characteristics:	
Grade 1a	Non-invasive tumor
Grade 1b	Non-invasive and proliferative tumor
Grade 2a	Invasive tumor
Grade 2b	Invasive and proliferative tumor
Grade 3	Metastatic tumor (cerebrovascular or systemic metastases)

High-power field: 0.30 mm^2, 400× magnification.
ACTH: corticotropic hormone; FSH: follicle-stimulating hormone; GH: growth hormone; LH: luteinizing hormone; PRL: prolactin; MRI: magnetic resonance imaging; TSH: thyroid-stimulating hormone.

ing response of somatotropinomas and NFPAs to treatment with somatostatin analogues. There is still no consistent evidence to include them in acromegaly treatment algorithms for selecting the first step of medical treatment. Thus, their use is currently restricted to research or specific cases.[2,16]

Among other interesting markers, RKIP protein levels significantly correlate to the response of serum GH and IGF-1 levels and, as a consequence, low RKIP expression levels and lack of RAF kinase inhibition are associated with a poorer response to somatostatin analogues in somatotropinomas.[57] Expression of the *AIP* gene is relevant in the diagnosis of isolated familial pituitary adenomas, and also in the therapeutic response of somatotroph adenomas.[58]

In recent years, other cell proliferation, apoptosis, and angiogenic markers, oncogenes, tumor suppressor genes, cell cycle mediators, long non-coding microRNAs and RNAs have been identified that participate in tumorigenesis, migration, proliferation, and invasive capacity of pituitary adenomas have been identified.[59]

However, no reliable morphological markers that predict PitNET recurrence are yet available. Recent research has provided new insights into the genesis and biological behavior of these tumors. The molecules explored include the TACSTD family (*EpCAM, TROP2*), neuropiline (*NRP-1*), oncogene-induced senescence (OIS), faskines (*FSCN1*), genes associated with invasion (*CLDN7, CNTNAP2, ITGA6, JAM3, PTPRC*, and *CTNNA1) EZH2*, and *ENC1* and *endocan* genes.[60] Molecular techniques, bioinformatics, and new drug options are useful tools for expanding understanding of the complex nature of pituitary tumorigenesis.[51,59,61] As their clinical value is established, they will have to be included in the pathology report.

Conclusions

Understanding of PitNETs has increased exponentially in recent years due to greater specificity of antibodies to adenohypophyseal hormones, gradual introduction of PTF measurement, and new advances in molecular biology. Overall, these advances currently allow for adequate typing of different subtypes of PitNETs in more than 95% of cases, which promotes their treatment and follow-up. In addition, the possibility of measuring transcription factors allows for a sequential pathological study strategy different than the one used to date. If the strategy proposed in this article is shown to be effective, it will mean significant savings in time and cost of reagents. It is therefore necessary to update the report to be issued by pathology services to help clinicians in optimal management of PitNETs.

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Conflicts of interest

AP has participated in clinical trials related to pituitary disease sponsored by Pfizer, Novartis, and Ibsen, and in dissemination of knowledge at symposia and meetings sponsored by Pfizer, Novartis, and Ibsen. GM has received speaker fees from Novo Nordisk and Lilly and support for attendance to meetings from Pfizer and Menarini. MPD has received research support grants from Pfizer and Novartis, and has received fees as speaker from Ipsen and as consultant from Recordati. IAL, MAJ, OT and RML have no conflicts of interest to declare.

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