

## REVIEW

# Pituitary carcinoma: reclassification and implications in the NET schema

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## Abstract

The entity known as pituitary carcinoma has been traditionally defined as a tumor of adenohypophysial cells that metastasizes systemically or craniospinally independent of the histological appearance of the lesion. Reported cases of pituitary carcinoma have clinically and histologically resembled their non-metastatic counterparts that were classified as adenomas; the majority of cases were initially diagnosed as adenomas, and with tumor progression and spread, the diagnosis was changed to carcinoma. This classification has been challenged since the definition of malignancy in most organs is not based only on metastatic spread. The extent of local invasion resulting in an inability to completely resect an adenohypophysial tumor can have serious consequences that can cause harm and are therefore not benign. To address this dilemma, it was proposed that pituitary tumors be classified as neuroendocrine tumors. This change in nomenclature is totally appropriate since these tumors are composed of classical neuroendocrine cells; as with other neuroendocrine tumors, they have variable behavior that can be indolent but can involve metastasis. With the new nomenclature, there is no requirement for a distinction between adenomas and carcinomas. Moreover, the WHO/IARC has provided an overarching classification for neuroendocrine neoplasms at all body sites; in this new classification, the term 'neuroendocrine carcinoma' is reserved for poorly differentiated high-grade malignancies that are clinically, morphologically and genetically distinct from well-differentiated neuroendocrine tumors. It remains to be determined if there are true pituitary neuroendocrine carcinomas.

## Key Words

- ▶ pituitary
- ▶ adenoma
- ▶ neuroendocrine tumor
- ▶ carcinoma
- ▶ invasion
- ▶ metastasis

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## Introduction

The pituitary is an endocrine gland composed of epithelial neuroendocrine cells that produce peptide hormones which regulate many aspects of homeostasis including growth, metabolism and reproduction. The seven normal neuroendocrine cell types are highly differentiated in structure and function. They are represented by members of three lineages dictated by expression of the transcription factors, PIT1, TPIT and SF1, and additional transcription factors ER $\alpha$  and GATA3, that regulate hormone synthesis

(Asa & Perry 2020, Asa *et al.* 2021b). These neuroendocrine cells can give rise to pituitary neuroendocrine tumors (PitNETs) that generally are well differentiated and reflect normal cytology, but may also be composed of immature cells that do not exhibit normal cytodifferentiation. PitNETs have been the subject of intense investigation and have been classified in a highly elaborate scheme that has been shown to be of value in diagnosis, prognosis and prediction of therapeutic response (Table 1).

**Table 1** Classification of PitNETs.

Family	Tumor type	Tumor subtype	Transcription factor(s)	Hormones	Other biomarkers
TPIT	Corticotroph	Densely granulated Sparsely granulated Crooke cell	TPIT	ACTH	Keratins Keratins Keratin rings
PIT1	Somatotroph	Densely granulated Sparsely granulated	PIT1	GH, αSU GH	Keratins Keratin fibrous bodies
	Lactotroph	Sparsely granulated Densely granulated	PIT1, ER	PRL PRL	(Keratins) (Keratins)
	Mammomatotroph		PIT1, ER	GH>PRL	Keratins
	Mature plurihormonal		PIT1, ER, GATA3	GH>PRL, TSH	Keratins
	Immature PIT1-lineage		PIT1 (ER, GATA3)	(GH, PRL, TSH)	(Keratins ± fibrous bodies)
SF1	Acidophil stem cell		PIT1, ER	PRL> GH	(Keratins ± fibrous bodies)
	Thyrotroph		PIT1, GATA3	TSH	(Keratins)
	Gonadotroph		SF1, GATA3	FSH, LH	(Keratins ± follicular cells)
?	Null cell Unclassified plurihormonal		TPIT/PIT1/SF1 combinations	ACTH/GH/PRL/TSH/ FSH/LH	(Keratins) Variable

The behavior of PitNETs is extremely variable. Some are slow-growing small tumors that may be incidental findings or may be detected because of their role in creating hormone excess syndromes (Fig. 1), while others are rapidly growing and invasive tumors that involve vital structures around the sella turcica that surrounds the pituitary (Fig. 2). Some respond well to medical therapy or can be completely resected surgically; others are inoperable and require ancillary therapies including radiotherapeutic and pharmacologic approaches to restrain both tumor growth and hormone hypersecretion.

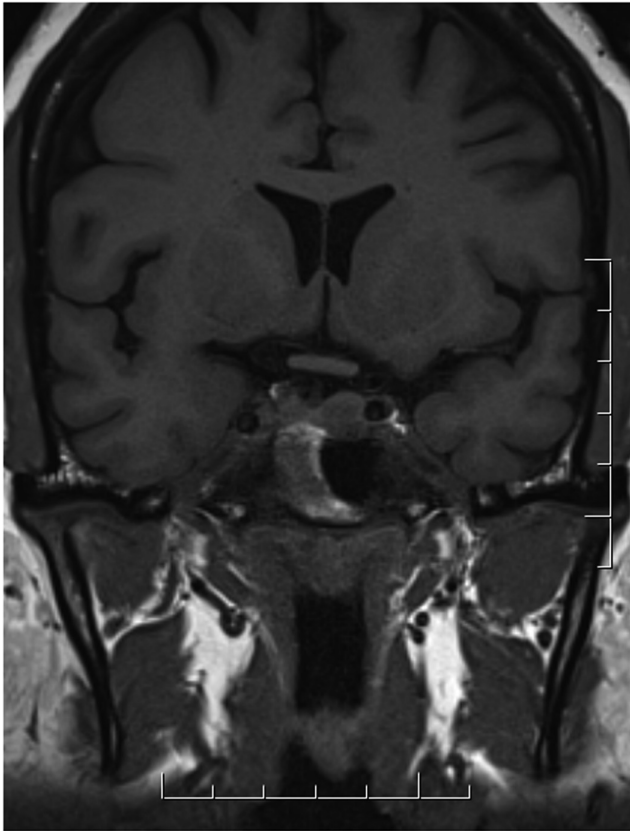
The terminologies used for these neoplasms have undergone changes due to clarification of definitions and in accordance with the recent WHO/IARC proposal for a common classification framework for all neuroendocrine neoplasms (Rindi *et al.* 2018).

### Historical definitions

The traditional classification of pituitary tumors identified the majority of neoplasms as adenomas. The criteria for a diagnosis of malignancy, called pituitary carcinoma, were very strict and required proof of systemic or craniospinal metastasis with no direct spread. In some previous classifications, there was a category of ‘atypical adenoma’ that was used to describe an invasive tumor with an elevated mitotic count, a Ki67 labeling index >3% and/or diffuse positive staining for p53 but no metastasis. However, the

application of these criteria was inconsistent and failed to predict the most aggressive tumors (Asa & Ezzat 2016). Other proposals have tried to account for invasion and proliferation to predict the probability of post-operative complete remission or tumor progression (Trouillas *et al.* 2013, Raverot *et al.* 2015). These approaches failed to deal with the fundamental fact that almost any PitNET can be invasive of surrounding structures including surrounding adenohypophysis, therefore even small tumors can recur despite apparent complete resection and large tumors are often unresectable due to invasion into the cavernous sinus and around the carotid arteries and/or upwards invasion into the brain (Asa & Ezzat 2016). The application of a cut-off of 3% for the Ki67 labeling index has not been reproducible nor does it consistently associate with invasiveness and recurrence (Asa & Ezzat 2016, Mete *et al.* 2018).

The problem with this traditional approach is that tumors classified as adenomas are not always benign in behavior (Figs 3, 4 and 5). The term ‘benign’ means not harmful in effect and this does not apply to many pituitary tumors that are not metastatic. Moreover, the definition of ‘malignant’ is used to describe neoplasms that tend to invade normal tissues or recur after removal; it does not only imply metastatic behavior. Many pituitary tumor patients suffer from recurrent disease progression and growth, they require lifelong therapies that can be expensive and cause significant side effects as well as inconvenience, yet they are told that they have a benign problem and often do not



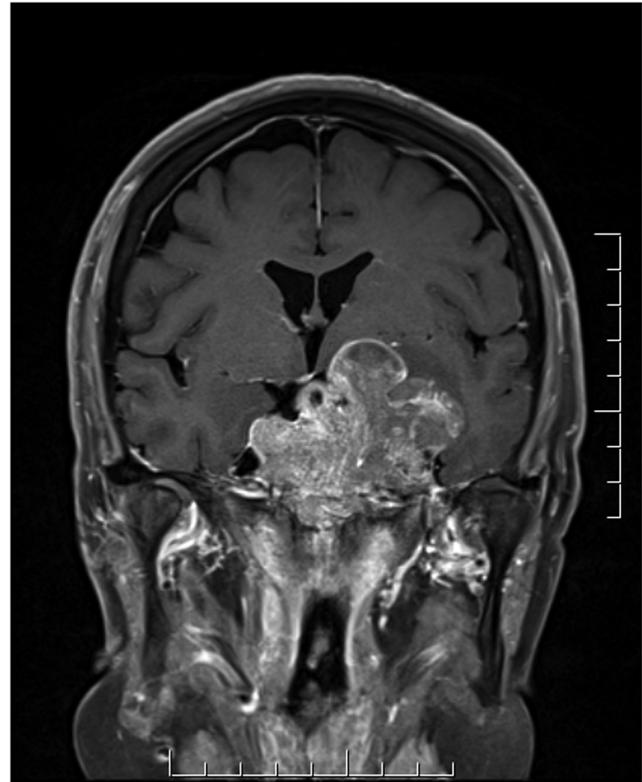
**Figure 1**  
MRI of intrasellar PitNET. The sella shows asymmetry with enlargement of the left side that contains a tumor distorting half of the pituitary.

receive the financial, psychosocial and healthcare support that they need and deserve.

The rationale for the traditional criteria is further challenged by the conundrum that most cases diagnosed as carcinoma are initially diagnosed as adenoma. These tumors clinically and histologically resemble non-metastatic tumors; while they may have high proliferative indices, this criterion alone is not able to predict metastasis, and thus far, there are no histologic, immunohistochemical or molecular features that can do so. Only with tumor progression and spread is the diagnosis changed to carcinoma, thus one is faced with a metastasizing adenoma, a contradictory term that cannot be supported.

### Current definitions

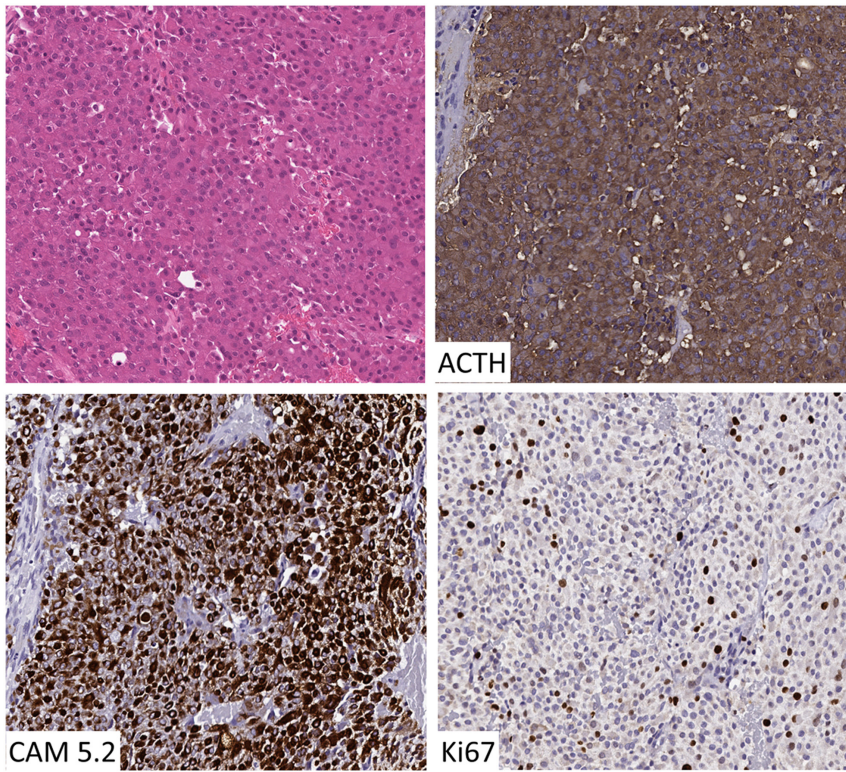
Neuroendocrine tumors (NETs) in other body sites have been recognized to show a spectrum of behavior that varies from indolent to aggressive. As an example, small bowel



**Figure 2**  
MRI of large invasive PitNET. There is a large heterogeneous soft tissue tumor mass encasing the optic nerves centered on the clivus, sella and skull base with exophytic suprasellar lobulations. It also encases the internal carotid arteries bilaterally. There is posterior displacement of the cerebral peduncle on the left side with elevation of the basal ganglia. There is also displacement of the left temporal lobe with milder posterior displacement of the left mid brain and pons.

NETs were initially called ‘carcinoid’ (meaning ‘carcinoma-like’) because they were described by Oberndorfer as lesions that looked like but were not carcinomas (Oberndorfer 1907). Subsequent evidence required a change in our understanding of these lesions that clearly have metastatic potential. NETs in different body sites have variable metastatic behavior ranging from the very rare spread of appendiceal NETs to the more common spread of small bowel and pancreatic NETs. Thus the terminology of ‘neuroendocrine tumor’ implies a well-differentiated neoplasm but with metastatic potential.

In 2017, the International Pituitary Pathology Club proposed to reclassify adenohypophysial tumors as PitNETs (Asa *et al.* 2017). This was followed by the WHO/IARC proposal for a common classification system for NETs at all body sites (Rindi *et al.* 2018); the pituitary proposal fits well within this framework. Despite some controversy, the proposal was adopted by the WHO fifth series; the first book to endorse this was the WHO classification of CNS

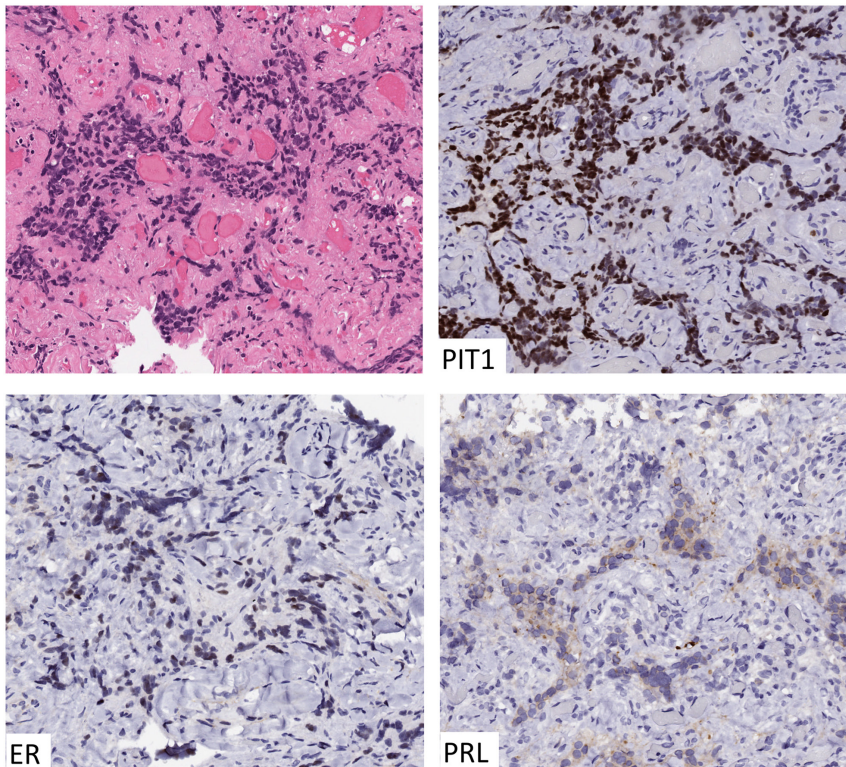


**Figure 3**

Histology of corticotroph tumor. This well-differentiated tumor with solid architecture is composed of cells with basophilic cytoplasm that stains intensely for ACTH and keratins (CAM 5.2). It presented in a middle-aged woman with Cushing disease, was resected surgically but recurred several times, eventually giving rise to distant metastasis and ultimately causing the patient's demise. The only unusual morphological finding was a Ki67 proliferation index that reached 10% in hotspots.

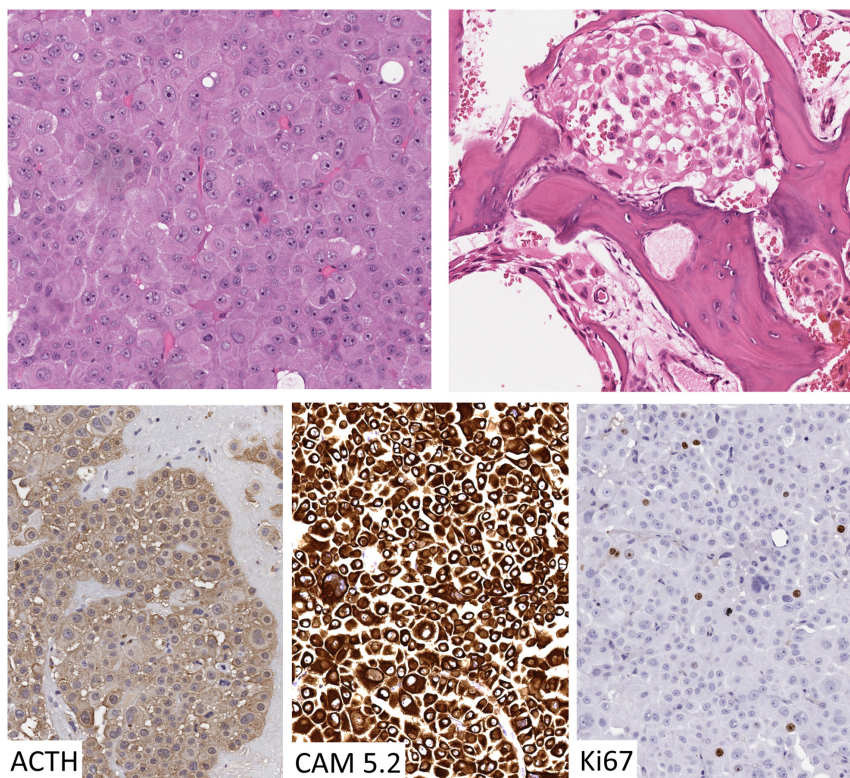
tumors (WHO Classification of Tumours Editorial Board 2021) in which the term PitNET was introduced following adenoma (i.e. adenoma/PitNET). In the following WHO classification of endocrine and neuroendocrine tumors

the terms are reversed, so that they are classified as PitNET/adenoma (WHO Classification of Tumours Editorial Board 2022), paving the way for the omission of the term 'adenoma' in the sixth series.



**Figure 4**

Histology of lactotroph tumor. This tumor that caused hyperprolactinemia was treated with dopamine agonist but continued to grow; it was resected surgically and had the typical morphology of a sparsely granulated lactotroph tumor with dopaminergic effects: the small tumor cells are trapped in a fibrovascular stroma, they show nuclear reactivity for PIT1 and ER, and there is scant cytoplasmic PRL. Despite two surgical sellar resections, she later developed metastases in brain and bone.



**Figure 5**  
Histology of Crooke cell tumor. This tumor is composed of large cells with abundant pale acidophilic hyaline cytoplasm that stains for ACTH with accentuation at the cell periphery and focally in the juxtannuclear area. The cytoplasm contains a striking ring-like intense positivity for keratins (CAM 5.2) corresponding to the hyaline material. This aggressive tumor with a Ki67 labeling index, that did not exceed 6%, invaded bony structures in and around the sella and ultimately caused the demise of the patient but there was no evidence of metastatic spread.

With the new terminology, there is no longer a need for the distinction of adenohypophysial carcinomas based strictly on metastatic spread; instead, lesions that spread are classified as ‘metastatic PitNETs’, obviating the need for a change in diagnosis when metastatic disease occurs.

The term carcinoma now has other implications, since the WHO/IARC proposal has recommended a clear distinction between well-differentiated NETs that generally harbor a specific pattern of molecular alterations (Asa *et al.* 2021a) and the poorly differentiated high-grade malignancies, classified as neuroendocrine carcinomas (NECs) that tend to have mutations in oncogenes and tumor suppressor genes that are the basis for adenocarcinomas in non-endocrine organs (Uccella *et al.* 2021). In the examples that have been studied carefully, this distinction can generally be identified by histological features as well as biomarkers of the mutational status. Most NECs have very high proliferation rates and are composed of cells that lack clear structural evidence of neuroendocrine differentiation but can express the common immunohistochemical biomarkers of neuroendocrine differentiation: INSM1, synaptophysin and, less so, chromogranins. Such tumors are very unusual as primary lesions in the pituitary; only recently has there been a report suggesting the possibility of a true primary pituitary NEC (Saeger *et al.* 2021).

### Epidemiology of PitNETs

Like other NETs (Yao *et al.* 2008), PitNETs are now being diagnosed as more common disorders than initially thought. Adenohypophysial tumors have been described as incidental findings in 22.5–27% of routine autopsies (Costello 1936, Burrow *et al.* 1981) and approximately 20% of radiological studies (Elster 1993, Ezzat *et al.* 2004). While most of these apparently incidental findings have been considered to be clinically non-functioning, larger lesions can cause hypopituitarism (Freda *et al.* 2020), immunohistochemical studies have shown that many produce prolactin (Kovacs *et al.* 1980, McComb *et al.* 1983); occasional supposedly ‘incidental’ lesions are somatotroph or corticotroph tumors that can be associated with undiagnosed clinically relevant disease. More recent population studies have shown that the prevalence of clinically diagnosed pituitary tumors ranges from approximately 78–116 cases per 100,000 people (Daly *et al.* 2006, Fontana & Gaillard 2009, Fernandez *et al.* 2010, Agustsson *et al.* 2015). The annual incidence is about 3.9/100,000 people (Tjornstrand *et al.* 2014); one study did a tumor-type analysis of annual incidence that identified 3.5 non-functioning, 1.6 lactotroph, 0.5 somatotroph and 0.2 corticotroph or thyrotroph tumors per 100,000

population per annum (Oh *et al.* 2021). Tumors causing hyperprolactinemia are consistently the most common PitNETs (Ezzat *et al.* 2004, Daly *et al.* 2006, Fontana & Gaillard 2009, Fernandez *et al.* 2010, Tjornstrand *et al.* 2014, Agustsson *et al.* 2015, Daly & Beckers 2020); since they are usually treated medically (Wilson & Dempsey 1978, Kovacs & Horvath 1986, Klibanski & Zervas 1991, Terada *et al.* 1995), the statistics are not reliably captured; so their exact incidence is unknown. Surgical resection is performed in over half of diagnosed patients (Daly *et al.* 2006). Among surgically resected PitNETs, more than a third are hormonally inactive tumors of SF1 lineage (Feldkamp *et al.* 1999, Mete *et al.* 2018), about 30% are of PIT1 lineage (more than half of those give rise to growth hormone excess) and approximately 15% are TPIT lineage tumors (Wilson & Dempsey 1978, Kovacs & Horvath 1986, Mindermann & Wilson 1994, Daly *et al.* 2006, Fernandez *et al.* 2010, Mete *et al.* 2018).

Metastatic behavior is exceptionally rare. Most reports publish single cases; the largest series includes 40 patients (McCormack *et al.* 2018). Metastatic PitNETs represented only 0.12% of the pituitary tumors in the German Pituitary Tumor Registry (Saeger *et al.* 2007) and 0.4% of surgically resected PitNETs in a published surgical series (Alshaikh *et al.* 2019). Metastases have been reported in patients of all ages, usually adults but a pediatric case has been reported (Guzel *et al.* 2008).

## Molecular pathology of PitNETs

Like small bowel NETs (Karpathakis *et al.* 2016), the underlying basis for tumorigenesis in the vast majority of sporadic PitNETs falls broadly into epigenetic changes (Ezzat *et al.* 2018, Asa *et al.* 2021c) that include classical promoter methylation, histone tail modifications and non-coding RNAs (Bahreini *et al.* 2021, Gossing *et al.* 2021). A subset of sporadic somatotroph tumors harbor activating mutations of *GNAS* that result in constitutive activation of cyclic AMP signaling and some corticotroph tumors have mutations of the *USP8* or *USP48* genes (Ezzat *et al.* 2018, Asa *et al.* 2021c); occasional aggressive corticotroph tumors have been shown to harbor mutations in *ATRX* (Casar-Borota *et al.* 2021), similar to pancreatic NETs. A minority of PitNETs are caused by genetic changes that fall into the group of germline mutations linked with familial endocrine syndromes and associated with other NETs. These include multiple endocrine neoplasia types 1, 4 and 5 due to mutations in *MEN1*, *CDKN1B* and *MAX*,

respectively, all of which are implicated in the development of NETs in other organs (Ezzat *et al.* 2018, Asa *et al.* 2021c). An unusual *MEN1*-like patient with acromegaly and hyperparathyroidism was attributed to germline mutation of *CDC73* (Nachtigall *et al.* 2020). Rare PitNETs have been described in patients with mutations in genes encoding the various components of the succinate dehydrogenase complex. These genetic alterations are similar to those found in other NETs. Other familial genetic predisposition syndromes include Carney complex due to germline mutations in the *PRKAR1A $\alpha$*  gene and the familial isolated pituitary adenoma syndromes attributed in about 50% of families to germline mutations in the *AIP* gene that encodes the aryl hydrocarbon-interacting protein. Recent evidence suggests a complex picture where components of heritable syndromes may be functionally important indirectly in sporadic tumors; the *MEN2* syndrome associated *RET* proto-oncogene was shown to be involved in an apoptosis-dependent manner in *AIP*-deficient somatotroph tumors (Garcia-Rendueles *et al.* 2021). However, PitNETs generally have not been shown to carry mutations in classical proto-oncogenes. Rare aggressive and metastatic tumors have mutations in *TP53* (Saeger *et al.* 2021, Uzilov *et al.* 2021) and may represent examples of tumors that qualify as NECs in the new WHO classification scheme.

## Therapy of PitNETs

The management of PitNETs generally follows the guiding principles adopted for NETs of other body sites. This includes surgical eradication wherever technically feasible (Asa *et al.* 2021b). However, in the case of aggressive PitNETs and carcinomas, this goal is often not achievable. As such adjuvant therapies are often employed. These include systemic analogs of dopamine (Greenman & Bronstein 2021) and somatostatin (Asa *et al.* 2021b) that typically reduce hormone production and effectively diminish tumor progression. However, the more rapidly growing and/or invasive PitNETs often require additional approaches. Targeted therapies relying on mTOR signaling (Monsalves *et al.* 2014) with everolimus or multikinase inhibitors such as sunitinib represent the next level of PitNET pharmacotherapy (Alshaikh *et al.* 2019). For those PitNETs that evade such agents the use of the DNA methylation inhibitor temozolomide without or with capecitabine as part of the CAP/TEM combination chemotherapy has become a mainstay (Ishida *et al.* 2022). The application of peptide receptor radiotherapy

taking advantage of somatostatin analog to chaperone intracellular delivery of beta-emitting lutetium 177 (Lu177) has also been reported for pituitary carcinomas (Alshaikh *et al.* 2019, Giuffrida *et al.* 2019). Progress in this strategic area of radiopharmaceuticals will undoubtedly facilitate the development of more potent agents for managing refractory PitNETs.

## Future directions

The addition of PitNETs to the common classification system of NETs has brought to the fore the question of **grading** these tumors. Other NETs are classified into three grades based on their proliferation index, either mitotic count or Ki67 labeling. However, while some previous studies that address these biomarkers in pituitary tumors have shown some correlation with tumor size, invasiveness, recurrence and metastasis (Landolt *et al.* 1987, Knosp *et al.* 1989, Thapar *et al.* 1996, Salehi *et al.* 2009) other authors have not (Wierinckx *et al.* 2007, Salehi *et al.* 2009, de Aguiar *et al.* 2010, Zada *et al.* 2011, Mete *et al.* 2012, 2018, Tortosa & Webb 2016) and one study identified a Ki67 of 1.5% as the cut-off for more aggressive clinical follow-up (Chiloiro *et al.* 2014). There is clear evidence that tumor subtype is a more valuable predictor of tumor behavior in the pituitary (Gomez-Hernandez *et al.* 2015, Asioli *et al.* 2019, Asa *et al.* 2021b) and this model has also been shown to be valuable in other NETs such as pancreas and rectum (Asa *et al.* 2021b). Further work will be required to show whether tumor grade or subtype is more important for other NETs.

Given that adenohypophysial tumors were considered to be benign, there was never any need for a **staging system**. However, the change in terminology brings with it a recognition that these tumors deserve some attention to prognostic features that can predict long-term outcomes (Asa 2021). As indicated by previous surgical data, the extent of invasion including the degree of lateral extension into the cavernous sinus (Knosp classification) (Knosp *et al.* 1993) and also the degree of extra-sellar and vertical extension into supra-sellar regions (Hardy classification) (Hardy 1973) have value in predicting future requirements for multimodal therapies including repeat operations and/or radiotherapy (Mete *et al.* 2012, Tampourlou *et al.* 2017). Clearly, metastatic disease alters the prognosis even further. Thus, there is an opportunity to develop an evidence-based staging system based on tumor size and extent of invasion as well as the rare spread to lymph nodes and metastatic spread, both intracranially and systemically.

The approach to diagnosis of PitNETs should follow that used for other neoplasms that have any malignant potential, including **synoptic reporting**. This has been proposed (Nose *et al.* 2011, Villa *et al.* 2019) but is not currently the standard of care. Finally, the addition of PitNETs to the family of NETs should result in improved data collection in **tumor registries**.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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## Consent for publication

All authors consent to publication.

## Author contribution statement

Conception and design: S L A, S E; data collection and analysis: S L A, S E; manuscript preparation and editing: S L A, S E; approval of final manuscript: S L A, S E.

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