Pituitary Carcinoma: Reclassification and Implications in the NET Schema

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Running Title: Pituitary Tumor Classification

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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
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 ERα and GATA3, that regulate hormone synthesis (Asa et al. 2021b; Asa and Perry 2020). 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).

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 (Figure 1), while others are rapidly growing and invasive tumors that involve vital structures around the sella turcica that surrounds the pituitary (Figure 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 described 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 and Ezzat 2016). Other proposals have tried to account for invasion and proliferation to predict the probability of post-operative complete remission or tumor progression (Raverot et al. 2015; Trouillas et al. 2013). 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 (Figures 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 to 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 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 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, Klimstra, Abedi-Ardekani, Asa, Bosman, Brambilla, Busam, de Krijger, Dietel, El-Naggar, Fernandez-Cuesta, Kloppel, McCluggage, Moch, Ohgaki, Rakha, Reed, Rous, Sasano, Scarpa, Scoazec, Travis, Tallini, Trouillas, van Krieken, & Cree 2018); the pituitary proposal fit well within this framework. Despite some controversy, the proposal was adopted by the WHO 5th series; the first book to endorse this was the WHO classification of central nervous system 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 6th series.

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, synaptophysisin 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% to 27% of routine autopsies (Burrow et al. 1981; Costello 1936) and approximately 20 percent 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 to 116 cases per 100,000 people (Agustsson et al. 2015; Daly et al. 2006; Fernandez et al. 2010; Fontana and Gaillard 2009). 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 thyrrotroph tumors per 100,000 population per annum (Oh et al. 2021). Tumors causing hyperprolactinemia are consistently the most common PitNETs (Agustsson, Baldvinsdottir, Jonasson, Olafsdottir, Steinthorsdottir, Sigurdsson, Thorsson, Carroll, Korbonits, & Benediktsson 2015; Daly, Rixhon, Adam, Dempegioti, Tichomiroma, & Beckers 2006; Daly and Beckers 2020; Ezzat, Asa, Couldwell, Barr, Dodge, Vance, & McCutcheon 2004; Fernandez, Karavitaki, & Wess 2010; Fontana & Gaillard 2009; Tjornstrand, Gunnarsson, Evert, Holmberg, Ragnarsson, Rosen, & Filipsson 2014); since they are usually treated medically (Klibanski and Zervas 1991; Kovacs and Horvath 1986; Terada et al. 1995; Wilson and Dempsey 1978) the statistics are not reliably captured, so their exact incidence is unknown. Surgical resection is performed in over half of diagnosed patients (Daly, Rixhon, Adam, Dempegioti, Tichomiroma, & Beckers 2006). Among surgically resected PitNETs, more than a third are hormonally inactive tumors of SF1 lineage (Feldkamp et al. 1999; Mete, Cintosun, Pressman, & Asa 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 (Daly, Rixhon, Adam, Dempegioti, Tichomiroma, & Beckers 2006; Fernandez, Karavitaki, & Wess 2010; Kovacs & Horvath 1986; Mete, Cintosun, Pressman, & Asa 2018; Mindermann and Wilson 1994; Wilson & Dempsey 1978).

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 tumours in the German Pituitary Tumour 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 (Asa et al. 2021c; Ezzat et al. 2018) that include classical promoter methylation, histone tail modifications and non-coding RNAs (Bahrreini et al. 2021). A subset of sporadic somatotroph tumors harbor activating mutations of GNAS that results in constitutive activation of cyclic AMP signaling and some corticotroph
tumors have mutations of the *USP8* or *USP48* genes (Asa, Mete, & Ezzat 2021c; Ezzat, Cheng, & Asa 2018); 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 (Asa, Mete, & Ezzat 2021c; Ezzat, Cheng, & Asa 2018). 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 (SDH) 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 *PRKAR1Aα* gene and the familial isolated pituitary adenoma (FIPA) syndromes attributed in about 50% of families to germline mutations in the *AIP* gene that encodes the aryl hydrocarbon-interacting protein (AIP). 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 protooncogenes. Rare aggressive and metastatic tumors have mutations in TP53 (Saeger, Mawrin, Meinhardt, Wefers, & Jacobsen 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, Mete, Cusimano, McCutcheon, Perry, Yamada, Nishioka, Casar-Borota, Uccella, La Rosa, Grossman, & Ezzat 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 analogues of dopamine (Greenman and Bronstein 2021) and somatostatin (Asa, Mete, Cusimano, McCutcheon, Perry, Yamada, Nishioka, Casar-Borota, Uccella, La Rosa, Grossman, & Ezzat 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, Asa, Mete, & Ezzat 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 mainstay (Ishida et al. 2021). The application of peptide receptor radiotherapy (PRRT) taking advantage of somatostatin analog to chaperone intracellular delivery of beta-emitting lutetium 177 (Lu177) has also been reported for pituitary carcinomas (Alshaikh, Asa, Mete, & Ezzat 2019; Giuffrida et al. 2019). Progress in this strategic area of radiopharmaceuticals will undoubtedly facilitate 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 of 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 (Knosp et al. 1989; Landolt et al. 1987; Salehi et al. 2009; Thapar et al. 1996) other authors have not (de Aguiar et al. 2010; Mete et al. 2012; Mete, Cintosun, Pressman, & Asa 2018; Salehi, Agur, Scheithauer, Kovacs, Lloyd, & Cusimano 2009; Tortosa and Webb 2016; Wierinckx et al. 2007; Zada et al. 2011) 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 (Asa, Mete, Cusimano, McCutcheon, Perry, Yamada, Nishioka, Casar-Borotra, Uccella, La Rosa, Grossman, & Ezzat 2021b; Asloli et al. 2019; Gomez-Hernandez et al. 2015) and this model has also been shown to be valuable in other NETs such as pancreas and rectum (Asa, Mete, Cusimano, McCutcheon, Perry, Yamada, Nishioka, Casar-Borotra, Uccella, La Rosa, Grossman, & Ezzat 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 outcome (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 extrasellar 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, Ezzat, & Asa 2012; Tampourlou et al. 2017). Clearly metastatic disease alters 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.
References


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WHO Classification of Tumours Editorial Board. *WHO classification of central nervous system tumours*. 5th series, 2021. Lyon, France, IARC.

WHO Classification of Tumours Editorial Board 2022. *WHO classification of endocrine and neuroendocrine tumours*, 5th series. Lyon, France, IARC.


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Figure Legends

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.

Figure 2. MRI of large invasive PitNET. There is a large heterogeneous soft tissue tumor mass encasing the optic nerves centred 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.

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 high Ki67 proliferation index.

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 hyaloine cytoplasm that stains for ACTH with accentuation at the cell periphery and focally in the juxtanuclear 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 relatively high Ki67 labeling index invaded into bony structures in and around the sella and ultimately caused the demise of the patient but there was no evidence of metastatic spread.
Table 1. Classification of PitNETs

<table>
<thead>
<tr>
<th>Family</th>
<th>Tumor Type</th>
<th>Tumor Subtype</th>
<th>Transcription Factor(s)</th>
<th>Hormones</th>
<th>Other Biomarkers</th>
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<tr>
<td>TPIT</td>
<td>Corticotroph</td>
<td>Densely granulated</td>
<td>TPIT</td>
<td>ACTH</td>
<td>Keratins</td>
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<td></td>
<td>Sparsely granulated</td>
<td></td>
<td></td>
<td>Keratins</td>
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<td>Crooke cell</td>
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<td></td>
<td>Keratin rings</td>
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<td>PIT1</td>
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<td>Densely granulated</td>
<td>PIT1</td>
<td>GH, αSU</td>
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<td></td>
<td>Sparsely granulated</td>
<td></td>
<td>GH</td>
<td>Keratin fibrous bodies</td>
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<td>Lactotroph</td>
<td>Sparsely granulated</td>
<td>PIT1, ER</td>
<td>PRL</td>
<td>(Keratins)</td>
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<td></td>
<td>Densely granulated</td>
<td></td>
<td>PRL</td>
<td>(Keratins)</td>
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<td>Mammosomatotroph</td>
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<td>PIT1, ER</td>
<td>GH&gt;PRL</td>
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<td>Mature plurihormonal</td>
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<td>PIT1, ER, GATA3</td>
<td>GH&gt;PRL, TSH</td>
<td>Keratins</td>
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<td>Immature PIT1-lineage</td>
<td></td>
<td>PIT1 (ER, GATA3)</td>
<td>(GH, PRL, TSH)</td>
<td>(Keratins ± fibrous bodies)</td>
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<td>Acidophil stem cell</td>
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<td>PIT1, ER</td>
<td>PRL&gt; GH</td>
<td>(Keratins ± fibrous bodies)</td>
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<td>PIT1, GATA3</td>
<td>TSH</td>
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<td>Gonadotroph</td>
<td>SF1, GATA3</td>
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<td>ACTH/GH/PRL /TSH/FSH/LH</td>
<td>Variable</td>
</tr>
</tbody>
</table>
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299x393mm (38 x 38 DPI)
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