

# From pituitary adenoma to pituitary neuroendocrine tumor (PitNET)

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## Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET): An IPPC Proposal

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**29 Abstract**

30           The classification of neoplasms of adenohypophysial cells is misleading because of the  
31 simplistic distinction between adenoma and carcinoma based solely on metastatic spread and the  
32 poor reproducibility and predictive value of the definition of atypical adenomas based on  
33 detection of mitoses or expression of Ki-67 or p53. In addition, the current classification of  
34 neoplasms of the anterior pituitary does not accurately reflect the clinical spectrum of behavior.  
35 Invasion and regrowth of proliferative lesions, and persistence of hormone hypersecretion cause  
36 significant morbidity and mortality. We propose a new terminology, pituitary neuroendocrine  
37 tumor (PitNET), which is consistent with that used for other neuroendocrine neoplasms and  
38 which recognizes the highly variable impact of these tumors on patients.

39 Since the early work of Minkowski who attributed acromegaly to a pituitary tumor (1),  
40 neoplasms composed of pituitary adenohypophysial cells have been recognized as the cause of  
41 significant illness. However, Harvey Cushing attributed the term “adenoma” even to patients  
42 who died of their disease (2).

43 We now recognize that these neoplasms are complex and heterogeneous; they present  
44 multiple clinical manifestations, including a wide range of proliferative and invasive behaviors  
45 (3). Some are slowly-growing small lesions that are clinically insignificant, some are small or  
46 large hormonally active lactotroph tumors that respond to medical therapy with shrinkage and  
47 reduced hormone secretion, while other small and minimally proliferative lesions cause the  
48 severe metabolic dysfunction of Cushing’s disease or acromegaly. Many are large and invasive  
49 neoplasms that cause significant morbidity due to mass effects, with or without hormone excess  
50 syndromes. Traditional classifications only recognize malignancy, denoted as pituitary  
51 carcinoma, when there is evidence of distant metastasis or cerebrospinal spread (4). The attempt  
52 to classify a subgroup as “atypical adenomas” based on detection of mitoses or expression of Ki-  
53 67 or p53 (4) has proven to lack reproducibility and does not accurately predict recurrence or  
54 resistance to medical therapy (5). Recently, a clinicopathological classification with five grades  
55 identified Grade 2b tumors as those with a high risk of recurrence or progression (6;7).  
56 However, prediction of clinical aggressive behavior of these neoplasms, which occurs in  
57 approximately 10% of these tumors, remains debatable (8). The term “adenoma”, which defines  
58 a tumor as benign, does not seem appropriate to define aggressive and invasive pituitary tumors  
59 that cannot be resected and are refractory to therapy.

60 Patients and healthcare providers have long expressed frustration that these lesions are  
61 considered rare, benign, and inconsequential. In most jurisdictions they are not reported in cancer

62 registries. Pituitary patients are often denied access to and/or health insurance coverage for  
63 therapies that would be provided for “cancers”.

64 The International Pituitary Pathology Club, created in 1981, is a group of expert  
65 pathologists, endocrinologists, neurosurgeons and scientists who meet on a regular basis to  
66 discuss challenges and advances in the pituitary field. At the 14th meeting in Annecy, France in  
67 November 2016, the subject of classification of these lesions was, as usual, controversial.  
68 However, there was consensus on one important aspect: pituitary endocrine neoplasms exhibit a  
69 spectrum of behaviors that are not entirely benign and can cause significant morbidity, even  
70 when they are not metastatic.

71 We therefore propose a reclassification of these tumors to apply terminology that has  
72 been widely accepted in other neuroendocrine tumors (NETs) (4). Pituitary hormone-producing  
73 cells are members of the family of neuroendocrine cells, similar to those of pancreatic islets, as  
74 well as dispersed endocrine cells of the gastrointestinal and respiratory tracts. Over the last two  
75 decades, there have been terminology shifts that reflect the potential for malignant behavior of  
76 even the most bland of those neuroendocrine neoplasms. They evolved from “adenoma” to  
77 “tumor” to recognize the lack of predictability. We therefore propose that neoplasms of  
78 adenohypophysial cells be termed “pituitary neuroendocrine tumors”.

79 Like other neuroendocrine neoplasms, many primary adenohypophysial tumors are  
80 indolent; they may be controlled by long-term pharmacologic treatment (e.g. dopamine-agonist  
81 therapy in the case of lactotroph tumors) or are non-invasive and cured by surgery. However, a  
82 variable proportion may recur despite remission. In addition, a large proportion (40%) is  
83 invasive into the cavernous or sphenoid sinuses or cranial bones and cannot be totally removed  
84 by surgery. Moreover, some are resistant to the multiple medical treatments available, and are

85 considered to be clinically “aggressive”. The features distinguishing these behaviors are not  
86 entirely clear at this time and there is still no consensus on this matter. Moreover, there is no  
87 biomarker that can reliably predict malignancy as defined by metastatic spread. There is  
88 evidence that morphologic subtypes of pituitary neoplasms of the various cell lineages exhibit  
89 more aggressive behavior (8). It is also clear that invasive lesions which cannot be surgically  
90 resected are likely to result in considerable morbidity (7); some may require radiotherapy or are  
91 rapidly proliferative despite surgery, radiotherapy and/or medical therapy, requiring  
92 chemotherapy, for example temozolomide, or molecular targeted therapies. Accordingly,  
93 indications for novel therapies require elucidation of biomarkers that can guide personalized  
94 strategies.

95 This revision of nomenclature is not intended to negate the classification by morphologic  
96 cell type, but instead is intended to change the classification to “tumor” rather than “adenoma”,  
97 for example, a “sparsely granulated somatotroph tumor” rather than “sparsely granulated  
98 somatotroph adenoma”. The classification by morphologic cell type has been adopted by the  
99 World Health Organization (WHO) (4) and will remain in the next WHO classification that is  
100 underway. Although the new terminology of “tumor” replacing “adenoma” will not be  
101 incorporated in the 2017 WHO book, this change, as with previous terminologies that  
102 transitioned to “NETs”, will be gradually adopted in order to be included in the next edition. We  
103 hope that clarification of additional appropriate biomarkers will ultimately allow further  
104 refinement of the classification of pituitary neuroendocrine tumors.

105 The authors of this statement feel strongly that the time has come to reclassify clonal  
106 adenohypophysial proliferations under the umbrella of “pituitary neuroendocrine tumor”  
107 (PitNET), a term that emphasizes the biological spectrum of these common endocrine



108 neoplasms. Importantly, by analogy with other NETs, we encourage tumor registries to capture  
109 data on these tumors, thereby assisting efforts to clarify clinical and pathological features that  
110 can appropriately guide patient management. Pituitary neuroendocrine tumors are not simply  
111 endocrine diseases, but should be considered as tumors with endocrine manifestations within the  
112 context of oncology.

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