

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 adeno-hypophysial cells be termed “pituitary neuroendocrine tumors”.

79 Like other neuroendocrine neoplasms, many primary adeno-hypophysial 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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