Pituitary (2019) 22:569–573
https://doi.org/10.1007/s11102-019-00988-2

A tale of pituitary adenomas: to NET or not to NET

Pituitary Society position statement

Ken K. Y. Ho[1] · Maria Fleseriu[2] · John Wass[3] · Aart van der Lely[4] · Ariel Barkan[5] · Andrea Giustina[6] · Felipe F. Casanueva[7] · Anthony P. Heaney[8] · Nienke Biermasz[9] · Christian Strasburger[10] · Shlomo Melmed[11]

Published online: 30 September 2019

Keywords Pituitary adenoma · Neuroendocrine tumor · Tumor classification

Current and proposed change of classification

Anterior pituitary tumors arising from oral ectoderm-derived differentiated hormone-expressing lineages are classified according to cell type, size, location, secretory function and neoplastic behavior. The pathological classification of pituitary tumors has been driven by advances in physiology, cell biology and genetics. Almost all pituitary adenomas are benign neoplasms; extremely rarely, some may undergo malignant transformation, metastasizing to extracranial sites. An intermediate group of higher risk locally invasive adenomas are described as 'atypical' or 'aggressive' based on clinical features.

In the 2004 Classification of Endocrine Tumors, the World Health Organization (WHO) defined this latter group as *atypical pituitary adenomas* while retaining previous functional classification based on hormone immunohistochemistry [1]. A modification to the classification of pituitary adenomas was proposed in 2017 [2]. WHO recommended that the term *atypical pituitary adenoma* be dropped and that these higher risk adenomas be characterized by the extent of proliferative and invasive markers. The 2017 WHO also recommended that the functional classification based on hormone production be replaced by cell lineage designation defined from the immunohistochemistry of expressed pituitary transcription factors and hormones.

More recently, The International Pituitary Pathology Club, a group of experienced pathologists, endocrinologists, neurosurgeons, and scientists have proposed that pituitary adenomas be designated as pituitary neuroendocrine tumors (NETs) [3].

✉ Ken K. Y. Ho
k.ho@garvan.org.au

1 The Garvan Institute of Medical Research, St. Vincents Hospital, The University of New South Wales, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia

2 Departments of Medicine and Neurological Surgery, Pituitary Center, Oregon Health & Science University, Portland, OR, USA

3 Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

4 Pituitary Center Rotterdam, Endocrinology Section, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

5 Division of Endocrinology, University of Michigan Health System, Ann Arbor, MI, USA

6 Division of Endocrinology and Metabolism, San Raffaele University Hospital, Milan, Italy

7 Division of Endocrinology, Santiago de Compostela University and Ciber OBN, Santiago, Spain

8 Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

9 Division of Endocrinology and Center for Endocrine Tumors, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands

10 Department of Medicine for Endocrinology, Diabetes and Nutritional Medicine, Charité Universitätsmedizin, Berlin, Germany

11 Pituitary Center, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Why is a nomenclature change to NET proposed?

The Club contends that "pituitary endocrine neoplasms exhibit a spectrum of behaviors that are not entirely benign and can cause significant morbidity, even when they are not metastatic. Many are large and invasive neoplasms that cause significant morbidity due to mass effects, with or without hormone excess syndromes" [3]. They propose that "a reclassification of these tumors to apply terminology that has been widely accepted in other NETs." The proposed argument is that:

(i) The word pituitary 'adenoma' be replaced by 'tumor' to recognize some similarity to extra-pituitary NETs that may manifest unpredictable malignant behavior among the most seemingly bland NE neoplasms;
(ii) Pituitary hormone-producing cells are members of the family of neuroendocrine cells and should be renamed as pituitary NETs.

This proposal has also received support from an International Agency for Research on Cancer in a WHO Consensus Expert Panel Consensus proposal on a common classification framework for neuroendocrine neoplasms [4].

This proposition, which is based on some similarity in unpredictable proliferative behavior, seems reasonable at first glance, especially for the small subset of aggressive adenomas. However, further consideration raises important questions as to whether a seemingly innocuous proposed change in terminology intended to 'simplify' a field may not necessarily fulfill the intention, and may, in fact, elicit unintended anxiety-provoking consequences for patients.

Tumor and adenoma definitions

As defined by standard textbooks, a tumor is a non-specific word connoting a neoplasm, an abnormal growth of cells, which can either be benign or malignant. An adenoma is a benign tumor arising from glands in epithelial tissue. According to the Club proposal, the rationale for using 'tumor' is the recognition of similarities to NETs in 'unpredictable malignant behavior.' However, tumor is a non-specific term for a neoplasm. The connotation that tumors harbor unpredictable malignant behaviors brings an unwarranted change to a time-honoured definition.

Replacing 'adenoma' with 'tumor' creates additional ambiguity because it implies that pituitary adenomas do not necessarily originate from the glandular structures of epithelial tissues, evoking confusion and inaccuracies about their lineage origin. *If replacing adenoma with tumor is adopted, the proposal not only embeds a sinister tone to neutral nomenclature but could also wrongly denote that pituitary neoplasms may not arise from glandular epithelial tissue.*

Classification

The Pituitary Pathology Club contends that 'pituitary hormone-producing cells are members of the family of neuroendocrine cells' [3]. However, what constitutes an endocrine cell or a neuroendocrine cell is not discussed nor is the hierarchal classification within the endocrine system. The proposed classification as stated by the Pituitary Pathology Club is at variance with that of The European Taskforce on Endocrine Cancers. This group appropriately classifies tumors of the pituitary, adrenal cortex, thyroid and parathyroid glands as *separate from* 'neuroendocrine cancers,' which are, in turn, classified as a subset of endocrine cancers (https://www.endocrinecancer.eu/en/pages/statement).

The 2000 WHO Histological Typing of Endocrine Tumors refers to endocrine tumors of the adenohypophysis, adrenal cortex, adrenal and extra-adrenal paraganglia, parathyroid glands, pancreas, and gastrointestinal tract [5]. The term neuroendocrine tumor is conspicuous by its absence in this histological classification of endocrine tumors. In a 2004 review of NETs encompassing tumors of extra-adrenal paraganglia, parathyroid glands, pancreas, and gastrointestinal tract, the authors argue for adoption of the neuroendocrine (rather than endocrine) nomenclature because many endocrine tumors share 'a number of antigens with nerve elements' that characterize the neuroendocrine origin of the cells [6]. *Pituitary (and parathyroid) adenomas are appropriately not included as NETs in this review.*

According to the American Society of Clinical Oncology, a NET arises from 'specialized cells with traits of both hormone-producing endocrine cells and nerve cells.' The Mayo Clinic has a similar definition (https://www.mayoclinic.org/diseases-conditions/neuroendocrine-tumors/symptoms-causes/syc-20354132). Both state that NETs can occur in any part of the body but point to lungs, gastrointestinal tract, pancreas, and adrenal glands as common sites *with no mention of the pituitary gland*.

Clearly, there is lack of consensus and of consistency in terminology and definitions of these loosely related tumors. Self-driven proposals to change terms and definitions among stakeholders without presenting an evidence-based case based on cell biology, taxonomy, and clinical phenotype is producing confusion and obfuscation surrounding the distinction between endocrine and NETs.

Pituitary adenoma behaviour

An argument to classify pituitary adenomas as NETs evolved from dissatisfaction with the term 'atypical adenoma' used then to designate a group of adenomas manifesting unpredictable behavior and invasiveness. A pertinent matter for supporting a terminology change is the question as to how representative is so-called 'NET' behavior among pituitary neoplasms.

Unselected autopsy studies report a prevalence of pituitary adenomas in about 10% of the population [7]. This high prevalence is supported by imaging surveys with CT [8, 9] and MRI [10], with one reporting a prevalence as high as 40% [11] among unselected subjects. *However, the overwhelming number of pituitary adenomas detected at autopsy are clinically inapparent, and do not cause morbidity.* Population-based studies report that approximately 1 in 1000 in the community suffer from clinically significant health problems caused by pituitary adenomas [12–14]. A survey in Belgium reported that approximately 56% of their patients with clinically relevant pituitary adenomas undergo surgery [12]. What proportion of surgically treated patients harbor 'atypical' adenomas that demonstrate aggressive or invasive behaviour? The data from 1139 patients from 5 centers demonstrate that about 10% of these tumors exhibit atypical behavior [15–19] considered to possess NET-like characteristics [3]. *Classical oncogene mutations have not been encountered* [20] and *less than 0.2% of surgically-resected pituitary neoplasms are malignant* [21].

What fraction of pituitary adenomas cause substantial morbidity from invasive behavior? In a population of 1 million, approximately 100,000 harbor pituitary adenomas (10% prevalence). Of these, approximately 100 cause clinically significant morbidity (prevalence 1:1000) [12–14], of which about 56 (56%) go to surgery. Of these 56, 6 (10%) are atypical. Thus, 6 of 100 clinically significant pituitary adenomas and 6 of 100,000 pituitary adenomas manifest behavior that are NET-like, giving a prevalence of 6% and 0.006% respectively (Fig. 1). Furthermore, as prolactinomas, the most prevalent pituitary secreting adenomas, rarely undergo surgical resection, the true prevalence of NET-like behavior is likely much lower.

Can a case be made for designating *all* pituitary adenomas as NETs when only a very small fraction exhibits invasive behaviors akin to those of extra-pituitary NETs? Is there justification for designating the majority (94%) of clinically significant non-invasive pituitary adenomas as NETs? It is true that pituitary endocrine neoplasms exhibit a spectrum of behaviors that are not entirely benign and may sometimes cause significant morbidity, even when they are not metastatic. However, it is equally true that *the vast majority of pituitary adenomas (99.9%) are indolent, non-invasive benign neoplasms.*

Pituitary neuroendocrine tumors

As the neuroendocrine system is diffuse, tumors can arise in almost any organ of the body, although most commonly in the gastrointestinal and respiratory system. Intracranial NETs are extremely rare, and of the eight reported, *two are NETs of the pituitary* and sellar region, and six of the skull base [22]. The two reported pituitary NETs which caused substantial parasellar, neuro-ophthalmic, central nervous system symptoms exhibited pre-operative morbidity indistinguishable from a non-functioning pituitary macroadenoma

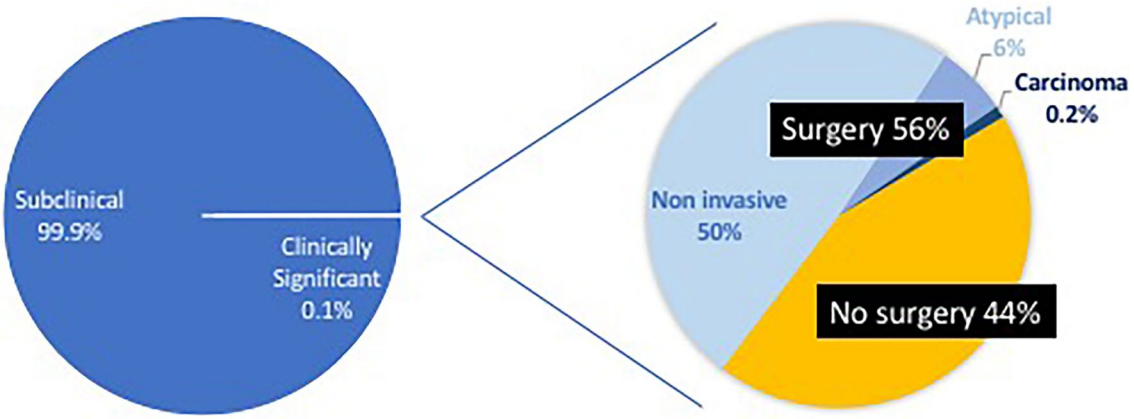

Fig. 1 Epidemiology of pituitary adenomas. Left panel, proportion of pituitary adenomas causing clinically significant health problems (0.1%) among all pituitary adenomas in the population. Right panel, proportion of pituitary neoplasms causing clinically significant health problems that do not require surgery (44%), the proportion requiring surgery (56%), and within the surgically operated adenomas, the proportions that are non-invasive (50%), atypical (6%), or cancerous (1%)

[22, 23]. These two tumors manifested high expression of cytokeratins, synaptophysin, and chromogranin A with high proliferative indices, fulfilling a histopathological diagnosis of NETs. These isolated case reports reinforce the rarity of extra-gastrointestinal and respiratory NETs under the traditional classification while reaffirming invasive and aggressive behavior.

Pituitary adenomas are a manifestation of multiple endocrine neoplasia type 1 (MEN1) along with parathyroid, carcinoid and pancreatic tumors. MEN1-associated pituitary adenomas emerge earlier, are larger, more invasive, and resistant to therapy [24]. Because of their syndromic link to carcinoid and gastro-pancreatic NETs, can MEN1-associated pituitary adenomas provide insights into refining the classification of pituitary adenomas?

What about other endocrine neoplasms?

If pituitary adenomas would be classified on the basis of neuroendocrine-like behavior as proposed, should the same classification also extend to other endocrine tumors, such as those of the thyroid and adrenal cortex? Follicular thyroid adenomas are common but occasionally exhibit aggressive and malignant behavior that cannot be predicted from histological markers of proliferative activity. Like pituitary adenomas, follicular thyroid neoplasms are classified as invasive or malignant based on histological and clinical findings. Similarly, adrenal cortical adenomas are common and are mostly benign neoplasms. A minority exhibit invasive and metastatic behavior similar to those of pituitary and thyroid neoplasms. Like pituitary adenomas, some thyroid follicular [25] and adrenal cortical neoplasms [26] express neuron-specific enolase and synaptophysin, considered neuroendocrine features. Based on the Pituitary Pathology Club suggestion, does the Club also propose that these tumors therefore be reclassified as thyroid NETs (as distinct from medullary thyroid carcinoma) and adrenal cortical NETs?

Perspective

Pathologists are invaluable members of an interdisciplinary team that aims to provide optimal management for pituitary neoplasms and related disorders [27]. Pathologists encounter a fraction of pituitary adenomas, i.e., only those that undergo surgery. Only a very small proportion of pituitary adenomas including those identified radiologically as an incidental finding ever end up under a microscope. *There is a clear selection bias in the 'pathological' degree of material that is sent to the pituitary pathologist*. The clinical epidemiology does not support the claim by the Club that "many are large and invasive neoplasms that cause significant morbidity" [3] or "that these tumors are recognized to have a high incidence of invasion of surrounding tissues" [4]. In fact, the contrary is true. Furthermore, health systems and patient psychological consequences arising from a terminology change to one that connotes a potentially grim prognosis are enormous and concerning. *Adopting a "NET" label for these benign adenomas engenders significant and unnecessary patient anxiety and confusion.* Pituitary adenomas are still best comprehensively classified based on cell lineage, transcription factor, and hormone expression, imaging characteristics, biochemical hormone secretory profile, and most importantly, clinical phenotype.

Simplification or confusion?

The Pituitary Pathology Club has argued a case for classifying all pituitary adenomas as pituitary NETs based on the behavior of a very small subgroup that exhibit behavior similar to those of extra-pituitary NETs.

The proposed change in classification by the Club creates a number of untoward challenges:

(i) Gives tumor a sinister connotation and removes meaningful information on its developmental origin;
(ii) Does not address the distinction between an endocrine cell and a neuroendocrine cell, possibly challenging the hierarchal classification of tumors of the endocrine system;
(iii) Asserts high-risk tumor behavior, despite that being an extremely rare exception for the vast majority of pituitary adenomas;
(iv) Has not addressed where very rare true NETs of the pituitary, sellar, and skull base sit in the proposed classification;
(v) Ignores whether similar terminology should apply to neoplasms in other endocrine organs, e.g., thyroid and adrenal.

We agree with the Pituitary Pathology Club's recognition of a small subgroup of high-risk adenomas that are not entirely benign and the need to subclassify these. However, adopting the nomenclature as proposed can only bring greater confusion. *The proposed NET nomenclature does not advance patient care, has little role in guiding decision-making, and will likely lead to unnecessary patient concerns.* The field requires a clear articulation of what distinguishes an endocrine tumor from a NET based on developmental origin and taxonomy and a consistency across organs and systems. The overwhelming majority of pituitary adenomas do not behave like NETs.

There is not yet a compelling case to call pituitary adenomas other than what they are.

Acknowledgements This position paper is co-authored by the Editors of *PITUITARY* and Officers of the Pituitary Society. No external or Society funding supported this work. The authors thank Shira Berman for outstanding editorial assistance.

References

1. WHO (2004) Pathology and genetics of tumours of endocrine organs. WHO classification of tumours, vol 8, 3 edn. WHO Press, Geneva
2. WHO (2017) WHO classification of tumours of endocrine organs. WHO classification of tumours, vol 10, 4 edn. WHO Press, Geneva
3. Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, Ezzat S, Grossman A, Ikeda H, Inoshita N, Karavitaki N, Korbonits M, Laws ER Jr, Lopes MB, Maartens N, McCutcheon IE, Mete O, Nishioka H, Raverot G, Roncaroli F, Saeger W, Syro LV, Vasiljevic A, Villa C, Wierinckx A, Trouillas J (2017) From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer 24(4):C5–c8. https://doi.org/10.1530/erc-17-0004
4. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Kloppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA (2018) A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) Expert Consensus proposal. Mod Pathol 31(12):1770–1786. https://doi.org/10.1038/s41379-018-0110-y
5. Solcia E, Kloppel G, Sobin LH (2000) Histological typing of endocrine tumours. World Health Organization international histological classification of tumours, 2nd edn. Springer, Berlin
6. Kaltsas GA, Besser GM, Grossman AB (2004) The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 25(3):458–511. https://doi.org/10.1210/er.2003-0014
7. Molitch ME (2017) Diagnosis and treatment of pituitary adenomas: a review. JAMA 317(5):516–524. https://doi.org/10.1001/jama.2016.19699
8. Chambers EF, Turski PA, LaMasters D, Newton TH (1982) Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. Radiology 144(1):109–113. https://doi.org/10.1148/radiology.144.1.7089241
9. Wolpert SM, Molitch ME, Goldman JA, Wood JB (1984) Size, shape, and appearance of the normal female pituitary gland. Am J Roentgenol 143(2):377–381. https://doi.org/10.2214/ajr.143.2.377
10. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH (1994) Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 120(10):817–820. https://doi.org/10.7326/0003-4819-120-10-199405150-00001
11. Chong BW, Kucharczyk W, Singer W, George S (1994) Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. Am J Neuroradiol 15(4):675–679
12. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A (2006) High prevalence of pituitary adenomas: a cross-sectional study in the Province of Liege, Belgium. J Clin Endocrinol Metab 91(12):4769–4775. https://doi.org/10.1210/jc.2006-1668
13. Fernandez A, Karavitaki N, Wass JA (2010) Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 72(3):377–382. https://doi.org/10.1111/j.1365-2265.2009.03667.x
14. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G, Thorsson AV, Carroll PV, Korbonits M, Benediktsson R (2015) The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. Eur J Endocrinol 173(5):655–664. https://doi.org/10.1530/eje-15-0189
15. Zada G, Woodmansee WW, Ramkissoon S, Amadio J, Nose V, Laws ER Jr (2011) Atypical pituitary adenomas: incidence, clinical characteristics, and implications. J Neurosurg 114(2):336–344. https://doi.org/10.3171/2010.8.Jns10290
16. Scheithauer BW, Gaffey TA, Lloyd RV, Sebo TJ, Kovacs KT, Horvath E, Yapicier O, Young Jr WF, Meyer FB, Kuroki T, Riehle DL, Laws Jr ER (2006) Pathobiology of pituitary adenomas and carcinomas. Neurosurgery 59(2):341–353; discussion 341–353. https://doi.org/10.1227/01.Neu.0000223437.51435.6e
17. Saeger W, Ludecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S (2007) Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 156(2):203–216. https://doi.org/10.1530/eje.1.02326
18. Yildirim AE, Divanlioglu D, Nacar OA, Dursun E, Sahinoglu M, Unal T, Belen AD (2013) Incidence, hormonal distribution and postoperative follow up of atypical pituitary adenomas. Turk Neurosurg 23(2):226–231. https://doi.org/10.5137/1019-5149.Jtn.6828-12.1
19. Chiloiro S, Doglietto F, Trapasso B, Iacovazzo D, Giampietro A, Di Nardo F, de Waure C, Lauriola L, Mangiola A, Anile C, Maira G, De Marinis L, Bianchi A (2015) Typical and atypical pituitary adenomas: a single-center analysis of outcome and prognosis. Neuroendocrinology 101(2):143–150. https://doi.org/10.1159/000375448
20. Melmed S (2011) Pathogenesis of pituitary tumors. Nat Rev Endocrinol 7(5):257–266. https://doi.org/10.1038/nrendo.2011.40
21. Raverot G, Jouanneau E, Trouillas J (2014) Management of endocrine disease: clinicopathological classification and molecular markers of pituitary tumours for personalized therapeutic strategies. Eur J Endocrinol 170(4):R121–R132. https://doi.org/10.1530/eje-13-1031
22. Nasi D, Perano D, Ghadirpour R, Iaccarino C, Servadei F, Romano A (2017) Primary pituitary neuroendocrine tumor: case report and literature review. Surg Neurol Int 8:101. https://doi.org/10.4103/sni.sni_450_16
23. Liu H, Wang H, Qi X, Yu C (2016) Primary intracranial neuroendocrine tumor: two case reports. World J Surg Oncol 14:138. https://doi.org/10.1186/s12957-016-0887-4
24. Marx SJ, Nieman LK (2002) Aggressive pituitary tumors in MEN1: do they refute the two-hit model of tumorigenesis? J Clin Endocrinol Metab 87(2):453–456. https://doi.org/10.1210/jcem.87.2.8289
25. Satoh F, Umemura S, Yasuda M, Osamura RY (2001) Neuroendocrine marker expression in thyroid epithelial tumors. Endocr Pathol 12(3):291–299
26. Haak HR, Fleuren GJ (1995) Neuroendocrine differentiation of adrenocortical tumors. Cancer 75(3):860–864. https://doi.org/10.1002/1097-0142(19950201)75:3%3c860:aid-cncr2820750318%3e3.0.co;2-g
27. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, Melmed S, Mortini P, Wass J, Giustina A (2017) Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a Pituitary Society statement. Pituitary 20(5):489–498. https://doi.org/10.1007/s11102-017-0838-2