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Pituitary neuroendocrine tumors (PitNETs): Nomenclature evolution, not clinical revolution

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Abstract:

Not Applicable

Dear Editor,

We read with interest "A tale of pituitary adenomas: to NET or not to NET" published in *Pituitary* [1]. The members of the International Pituitary Pathology Club (IPPC) who proposed the term "pituitary neuroendocrine tumor" (PitNET) [2] are Pathologists, Endocrinologists and Neurosurgeons who diagnose and treat patients with pituitary diseases. We proposed this change to address problems that result from classification of adenohypophysial-cell tumors as "adenomas". While new terminology generates challenges and may have unforeseen implications, it is our opinion that change is appropriate when there is a clinicopathological basis. Here we address a number of issues raised by Ho *et al*.

Ho *et al* suggest that the term tumor "embeds a sinister tone to neutral nomenclature". In fact, tumors may be benign or malignant; the term itself has no sinister connotation. Perhaps the concern is rather about "neuroendocrine tumor", which implies at least some potential for aggressive behavior. This is true in the pituitary, an argument in favor of the term PitNET. The use of "tumor" alone remains nonspecific, and includes other pituitary tumors that are not of adenohypophysial-cell derivation.

The Pituitary Society endorses the term "adenoma", because these tumors are "benign" in about 99.9% of cases. The Merriam–Webster dictionary defines benign as "of a mild type or character that does not threaten health or life", as "having no significant effect". The Oxford Medical Dictionary defines "benign" as "a tumour that does not invade and destroy the tissue in which it originates", a "disorder or condition that does not produce harmful effects". We respectfully emphasize that pituitary adenohypophysial-cell tumors may invade and destroy the tissue in which they originate as well as adjacent tissues, and have significant impact on patients' health and quality of life. It should also be noted that "malignant" is not restricted to neoplasms that metastasize; it also applies to tumors that invade adjacent structures.

The incidence of aggressive pituitary tumors is not entirely clear but is significantly higher than the 0.1% suggested by the Pituitary Society. Population studies(1) indicate that between 40 and 56% of patients with clinically-diagnosed adenohypophysial-cell tumors require surgery [3,4], and 23% of those have persistent disease that cannot be cured by surgery [5]. Non-functioning

tumors that fail primary treatment have >60% risk of progression at 5 years [6]. The IPPC proposal addresses the frustration of patients who have persistent pituitary tumors requiring expensive, life-long medical treatment and sometimes radiation, therapies that may not be readily available for patients with a "benign" disorder". The PitNET terminology avoids this clinical contradiction as well as that encountered when an "adenoma" develops metastasis.

The World Health Organization has proposed the term "neuroendocrine neoplasm" to describe neuroendocrine proliferations throughout the body [7] and distinguishes aggressive undifferentiated "neuroendocrine carcinoma" (NEC) from well-differentiated, generally low grade "neuroendocrine tumor" (NET). Our proposal for PitNET is consistent with this classification.

Interestingly, Ho et al argue that "replacing "adenoma" with "tumor" creates additional ambiguity because it implies that pituitary adenomas do not necessarily originate from the glandular structures of epithelial tissues". Contemporary understanding of NETs indicates that most derive from specialized neuroendocrine cells of glandular epithelium [7]. While other groups, including the European Taskforce on Endocrine Cancers, classify tumors of the pituitary, adrenal cortex, thyroid and parathyroid glands as separate from 'neuroendocrine', in our view this is incorrect. The pituitary and parathyroid glands are composed of epithelial cells whose main function (unlike thyroid follicular epithelium and adrenal cortical steroidogenic cells) is uptake of amines for processing into peptide hormones that are packaged into double membrane-bound "neurosecretory" granules where they are stored until they are secreted. These functional and morphological features, along with expression of neuroendocrine biomarkers such as chromogranins and somatostatin receptors, support the view that the hormone-secreting cells of the adenohypophysis are indeed neuroendocrine, as proposed many years ago by Ferrand, LeDouarin, Takor-Takor and Pearse.

We maintain that it is appropriate to define primary tumors of adenohypophysial cells as PitNETs. We emphasise that all NETs have variable clinico-pathologic characteristics, and that PitNETs, like other NETs, are heterogeneous in morphology, hormone production, proliferation and invasive behavior. In this respect, the proposed term "tumor" best reflects the heterogeneity and clinical spectrum of primary adenohypophysial neoplasms.

The change in terminology does not imply a change in the clinical responsibilities of members of the multidisciplinary care team that deals with patients. Rather, the change emphasises the need for an integrated approach that has evolved for all NETs, including the use of current and novel therapeutic paradigms that are common to these tumors at all sites.

Compliance with Ethical Standards:
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References

(1) Ho KKY, Fleseriu M, Wass J, van der Lely A, Barkan A, Giustina A, Casaneuva FF, Heaney AP, Biermasz N, Strasburger C, Melmed S (2019). A tale of pituitary adenomas: to NET or not to NET : Pituitary Society position statement. Pituitary, in press.

(2) 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: From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer 24(4):C5–C8 (2017).

(3) Tjornstrand A, Gunnarsson K, Evert M, Holmberg E, Ragnarsson O, Rosen T, Nystrom HF: The incidence rate of pituitary adenomas in western Sweden for the period 2001-2011. Eur J Endocrinol 171:519-526 (2014)

(4) Daly AF, Rixhon M, Adam C, Dempegioti A, Tichmirowa MA, Beckers A: High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 91:4769-75 (2006).

(5) Asioli S, Righi A, Iommi M, Baldovini C, Ambrosi F, Guaraldi F, Zoli M, Mazzatenta D, Faustini-Fustini M, Rucci P, Giannini C, Foschini MP: Validation of a Clinicopathological score for the Prediction of Post-Surgical Evolution of Pituitary Adenoma: Retrospective Analysis on 566 Patients from a Tertiary Care Centre. Eur J Endocrinol 180:127-134 (2019)

(6) Tampourlou M, Ntali G, Ahmed S, Arlt W, Ayuk J, Byrne JV, Chavda S, Cudlip S, Gittoes N, Grossman A, Mitchell R, O'Reilly MW, Paluzzi A, Toogood A, Wass JAH, Karavitaki N (2017) Outcome of Nonfunctioning Pituitary Adenomas That Regrow After Primary Treatment: A Study From Two Large UK Centers. J Clin Endocrinol Metab 102(6):1889-1897.

(7) 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.