From pituitary adenoma to pituitary neuroendocrine tumor (PitNET)
Asa, S L; Karavitaki, Niki

DOI:
10.1530/ERC-17-0004

License:
None: All rights reserved

Document Version
Peer reviewed version

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
This is not the definitive version of record of this article. This manuscript has been accepted for publication in Endocrine-Related Cancer, but the version presented here has not yet been copy edited, formatted or proofed. Consequently, the Society for Endocrinology accepts no responsibility for any errors or omissions it may contain. The definitive version is now freely available at: http://dx.doi.org/10.1530/ERC-17-0004 2017, Society for Endocrinology.

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
# Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET): An IPPC Proposal

<table>
<thead>
<tr>
<th>Journal:</th>
<th><em>Endocrine-Related Cancer</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>ERC-17-0004.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Unsolicited Commentary</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
</tr>
</tbody>
</table>
| Complete List of Authors: | Asa, Sylvia; University Health Network, Pathology  
Casar-Borota, Olivera; Uppsala University Hospital, Department of Clinical Pathology; Uppsala University, Department of Immunology, Genetics and Pathology  
Chanson, Philippe; Assistance Publique- Hôpitaux de Paris- CHU Bicêtre, Service d’Endocrinologie et Maladies de la Reproduction; Université Paris-Sud, UMR S693  
Delgrange, Etienne; Université Catholique de Louvain La Faculté de Médecine, Medicine  
Earls, Peter; St Vincent's Hospital, Pathology  
Ezzat, Shereen; University of Toronto, Medicine  
Grossman, Ashley; University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism  
Ikeda, Hidetoshi; Oharal center Hospital, Department of Neurosurgery  
Inoshiota, Naoko; Toranomon Byoin, Pathology  
Karavitaki, Niki; University of Birmingham, Endocrinology  
Korbonits, Marta; Barts and the London Medical School, Endocrinology  
Laws, Edward; BWH , NS;  
Lopes, M. Beatriz; University of Virginia, Pathology  
Maartens, Nicholas; Alfred Health, Neurosurgery  
McCutcheon, Ian; University of Texas MD Anderson Cancer Center, Neurosurgery  
Mete, Ozgur; University Health Network, Pathology  
Nishioka, Hiroshi; Toranomon Byoin, Neurosurgery  
Raverot, Gérald; Hospices Civils de Lyon, endocrinology; INSERM U1028; CNRS UMR5292; , Lyon Neuroscience Research Center, Neuro-oncology & Neuro-inflammation team  
Roncaroli, Frederico; University of Manchester, Pathology  
Saeger, Wolfgang; Universität Hamburg, Neuropathology  
Syro, Luis; Hospital Pablo Tobon Uribe and Clinica Medellin, Department of Neurosurgery  
Vasiljevic, Alexandre; Centre Hospitalier Universitaire de Lyon, Pathology  
Villa, Chiara; CHU de Liège, University of Liège, Department of Endocrinology  
Wierinckx, Anne; Cancerology Research Center of Lyon, INSERM U1052/CNRS UMR 5286; University of Lyon, University Lyon 1  
Trouillas, Jacqueline; université de lyon, lyon 1, faculté de médecine Lyon Est |
| Keywords: | pituitary tumors, nomenclature |
Pituitary Adenoma to Pituitary Neuroendocrine Tumor (PitNET):

An International Pituitary Pathology Club Proposal

Inoshita N, Karavitaki N, Korbonits M, Laws E.R. Jr, Lopes M.B., Maartens N, McCutcheon IE,
Wierinckx A, and Trouillas J

and the attendees of 14th Meeting of the International Pituitary Pathology Club, Annecy, France,
November 2016:


Running Title: Nomenclature revision for pituitary tumors

Correspondence to:

Sylvia L. Asa and Jacqueline Trouillas
Department of Pathology and Emeritus Professor
University Health Network and Faculty of Medicine Lyon-Est
University of Toronto and University of Lyon, France
200 Elizabeth Street, 11th Floor and Rue G. Paradin
Toronto, Ontario M5G 2C4 Canada and 69372 Lyon, France
Facsimile: 1-416-349-5517 and Email: Jacqueline.trouillas@univ-lyon1.fr
Email: sylvia.asa@uhn.ca

Disclosure Summary: The authors have nothing to disclose.

No funding was received for this work.
Abstract

The classification of neoplasms of adenohypophysial cells is misleading because of the simplistic distinction between adenoma and carcinoma based solely on metastatic spread and the poor reproducibility and predictive value of the definition of atypical adenomas based on detection of mitoses or expression of Ki-67 or p53. In addition, the current classification of neoplasms of the anterior pituitary does not accurately reflect the clinical spectrum of behavior. Invasion and regrowth of proliferative lesions, and persistence of hormone hypersecretion cause significant morbidity and mortality. We propose a new terminology, pituitary neuroendocrine tumor (PitNET), which is consistent with that used for other neuroendocrine neoplasms and which recognizes the highly variable impact of these tumors on patients.
Since the early work of Minkowski who attributed acromegaly to a pituitary tumor (1), neoplasms composed of pituitary adenohypophysial cells have been recognized as the cause of significant illness. However, Harvey Cushing attributed the term “adenoma” even to patients who died of their disease (2).

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

Patients and healthcare providers have long expressed frustration that these lesions are considered rare, benign, and inconsequential. In most jurisdictions they are not reported in cancer
registries. Pituitary patients are often denied access to and/or health insurance coverage for therapies that would be provided for “cancers”.

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

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

Like other neuroendocrine neoplasms, many primary adenohypophysial tumors are indolent; they may be controlled by long-term pharmacologic treatment (e.g. dopamine-agonist therapy in the case of lactotroph tumors) or are non-invasive and cured by surgery. However, a variable proportion may recur despite remission. In addition, a large proportion (40%) is invasive into the cavernous or sphenoid sinuses or cranial bones and cannot be totally removed by surgery. Moreover, some are resistant to the multiple medical treatments available, and are
considered to be clinically “aggressive”. The features distinguishing these behaviors are not entirely clear at this time and there is still no consensus on this matter. Moreover, there is no biomarker that can reliably predict malignancy as defined by metastatic spread. There is evidence that morphologic subtypes of pituitary neoplasms of the various cell lineages exhibit more aggressive behavior (8). It is also clear that invasive lesions which cannot be surgically resected are likely to result in considerable morbidity (7); some may require radiotherapy or are rapidly proliferative despite surgery, radiotherapy and/or medical therapy, requiring chemotherapy, for example temozolomide, or molecular targeted therapies. Accordingly, indications for novel therapies require elucidation of biomarkers that can guide personalized strategies.

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

The authors of this statement feel strongly that the time has come to reclassify clonal adenohypophysial proliferations under the umbrella of “pituitary neuroendocrine tumor” (PitNET), a term that emphasizes the biological spectrum of these common endocrine
neoplasms. Importantly, by analogy with other NETs, we encourage tumor registries to capture data on these tumors, thereby assisting efforts to clarify clinical and pathological features that can appropriately guide patient management. Pituitary neuroendocrine tumors are not simply endocrine diseases, but should be considered as tumors with endocrine manifestations within the context of oncology.

Acknowledgement

The authors acknowledge the participation and wise counsel of Prof. Günter Klöppel in the discussions that led to this manuscript.

References