

## Does New WHO 2022 Nomenclature of Pituitary Neuroendocrine Tumors Offer an Extra Edge to the Neurosurgeons for Its Management? A Narrative Review

Alok Srivastava<sup>1</sup> Manish Singh<sup>1</sup> Awadhesh Yadav<sup>2</sup> Chhitij Srivastava<sup>2</sup> Anil Chandra<sup>2</sup> Akanksha D. Srivastava<sup>3</sup>

<sup>1</sup>Department of Neurosurgery, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India

<sup>2</sup> Department of Neurosurgery, King George's Medical University, Lucknow, Uttar Pradesh, India

<sup>3</sup>Department of Paediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India

Asian J Neurosurg 2024;19:107–111.

#### Address for correspondence Alok Srivastava, MS, MCh, Department of Neurosurgery, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur 208002, Uttar Pradesh, India (e-mail: dralok.neurosurgeon123@gmail.com).

### Abstract

The new World Health Organization nomenclature of pituitary tumors was introduced in the year 2022 after much deliberation. This nomenclature clearly demarcates the anterior lobe (adenohypophyseal), posterior lobe (neurohypophyseal), and hypothalamic tumors. There is also focus on other tumors arising in the sellar region. The nomenclature has also advocated the routine use of immunohistochemistry in describing the pituitary transcription factors that plays a fundamental role in distinguishing the cell lineage of these tumors. However, the nomenclature is complex in understanding due to inclusion of pathological correlates like transcription factors, hormones, biomarkers, and various controversies that have emerged regarding the renaming of pituitary adenomas (PA) as PiTNETs ("Pituitary Neuroendocrine tumors") because majority of the adenomas are benign and have rare metastatic behavior while classifying them as PiTNETs will create unnecessary misinterpretation of these as aggressive tumors that will lead to apprehension among the patients. The new classification gives deeper insight into the histological picture of the various pituitary tumors but other than contributing to the follow-up strategy and postsurgery management, this classification does not add anything new that could be advantageous for the neurosurgeons in clinical practice and decision making, especially in deciding the plan of action for surgery. Hence, there is need of a more comprehensive, integrated, neuroradiological-based classification with more emphasis on the invasiveness of these tumors that would assist the neurosurgeons in planning the treatment strategy and managing patients of pituitary tumors.

**Keywords** 

► PITNETS

pituitary tumors

► WHO classification

pituitary adenomas

► management

article published online June 10, 2024 DOI https://doi.org/ 10.1055/s-0043-1777264. ISSN 2248-9614.  $\ensuremath{\mathbb{C}}$  2024. Asian Congress of Neurological Surgeons. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/ licenses/by-nc-nd/4.0/)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

### Introduction

Pituitary gland is a pea-sized complex structure located below the hypothalamus at the base of the skull in the sella turcica and is composed of three types of cells: first, adeno-hypophyseal, that is, anterior lobe hormone-secreting neuroendocrine cells; second, neurohypophyseal, that is, posterior lobe pituicytes that are comprised of modified glia, axonal extensions of hypothalamic neurons that secrete hormones into the bloodstream; third are the stromal cells that include meninges, blood vessels, bone, nerves, and other connective tissues.<sup>1</sup> Pituitary gland is the center of all the stimulating hormones of various organs; its overgrowth leads to hormone variances, like acromegaly, Cushing disease, central hypothyroidism, and hyperprolactinemia.<sup>2,3</sup>

Recently, the incidence of pituitary adenomas has increased. The reported prevalence of pituitary tumors varies with method of data acquisition. Autopsy studies yield a figure of 10.7%, while population-based studies reported 77.6 to 115.6 cases per 1,00,000 inhabitants. Pituitary tumors sum up for 10 to 15% of all intracranial neoplasms and is the third most common cranial tumor in adulthood. Pituitary adenoma is the most common (~85%) tumor in the sellar-suprasellar region.<sup>4</sup> Pituitary tumors can be either hormone nonsecreting or hormone secreting. Hormonally active tumors are characterized by excessive hormone secretion of prolactin in 69 to 80% of cases, growth hormone (GH) in 13 to 20%, adrenocorticotropic hormone (ACTH) in 5 to 10%, and thyroid-stimulating hormone (TSH) in 1 to 2%.<sup>5</sup>

Management of pituitary tumors is mainly focused on timely diagnosis and effectively controlling excessive hormone secretion as well as relieving the mass effect of the tumor bulk along with replacement of deficient hormones.<sup>6,7</sup> Neurosurgeons play a crucial role in the management of pituitary adenomas due to the local mass effect or clinical symptoms due to hormone excess that is adversely affecting the patient's life. The advent of novel molecular techniques for understanding the cellular differentiation mechanisms and transcription factors especially associated with pituitary tumors have provided a wider clarity in effective management of pituitary tumors.<sup>2,3</sup>

The new World Health Organization (WHO) 2022 nomenclature of pituitary tumors clearly demarcates the anterior lobe (adenohypophyseal), posterior lobe (neurohypophyseal), and hypothalamic tumors. There is also focus on other tumors arising in the sellar region. The nomenclature has also advocated the routine use of immunohistochemistry in describing the pituitary transcription factors that plays a fundamental role in distinguishing the cell lineage of these tumors.<sup>8,9</sup> A comparison of the newer and the previous classification has been shown in **– Table 1**.

However, the nomenclature is complex in understanding due to inclusion of pathological correlates like transcription factors, hormones, and biomarkers and various controversies that have emerged regarding the renaming of pituitary adenomas as pituitary neuroendocrine tumors (PiTNETs). Hence, this review has critically appraised the new WHO 2022 nomenclature of pituitary tumors to understand its relevance from a neurosurgeon's point of view that will serve as a guide for the other clinicians involved in the management of pituitary tumors in decision making and individualized patient management approaches.

### Evolution from "Pituitary Adenoma" to "Pituitary Neuroendocrine Tumor (PitNET)": The Dynamic Concept

Due to the complexity and heterogeneity of pituitary tumors, there has been an ever-changing view on the nomenclature of these tumors over the last few years. Initially, the WHO classification published in the year 2004 classified these adenohypophyseal tumors into seven main types: GH-, PRL-, FSH/LH-, ACTH-, and TSH-producing lesions based on their immunohistochemistry.<sup>10-12</sup> They were further sub-divided into 13 ultrastructural subtypes.<sup>11</sup>

Almost after a decade, in 2017, the WHO recognized the relevance of transcription factors that was lineage-restricted, to classify tumors of adenohypophyseal cells into three following lineages: PIT1 (pituitary-specific transcription factor 1), TPIT (pituitary cell restricted factor), and SF1 (splicing transcription factor 1).<sup>12,13</sup> Lactotroph, somatotroph, and thyrotroph belong to the PIT1 lineage, corticotroph to the TPIT lineage, and gonadotroph to the SF1 lineage. There were two major modifications, first, a futuristic approach was introduced using the adenohypophysial-cell lineages as transcription factors for a precise subclassification, especially the nonfunctioning adenomas.<sup>10</sup> Second, clinicopathological prognostic parameters were discussed for predicting the increase in risk and aggressiveness of adenomas.<sup>12</sup>

The members of the International Pituitary Pathology Club, in 2017, proposed the use of the term "neuroendocrine tumor" instead of "adenoma" to define tumors of adenohypophyseal cells.<sup>14–16</sup> Since then, there has been an ongoing debate over the proposal to this change in term as adenomas are benign, and tumors have a notorious effect on the surrounding structures in the brain.<sup>17</sup> It has been seen that approximately 40% of the tumors of pituitary gland invade the cavernous sinus and very less likely into bone. Hence, "Invasive adenoma" will be a contradictory term. Some experts of the WHO also proposed to include pituitary tumors in "neuroendocrine neoplasms" (NEN), which were further divided into the neuroendocrine carcinomas (NEC) for poorly differentiated, aggressive tumors, and the neuroendocrine tumors (NET) for the generally low-grade and well-differentiated neoplasms.<sup>18</sup> So, a proposal was made to reflect the more dynamic behavior of pituitary tumors (as invasiveness cause higher risk of recurrence) and may open new strategies for the early identification and management of the most aggressive forms.<sup>17</sup>

For such reasons, there was a change made in the terminology of pituitary adenomas by the WHO in 2022, that is, the 5th edition. Pituitary adenomas were named PitNETs. This was acceptable to form a uniform classification strategy for all neuroendocrine neoplasms.<sup>14</sup> Generally neuroendocrine tumors like PiTNETs have metastatic property that is

Points of comparison	4th edition, 2017	5th edition, 2022		
Time duration from previous classification	14 years after 2003	5 years after 2017		
Changes from previous edition	<ol> <li>Adenohypophyseal cell lineages for classi- fication and subtypes determined by transcription factors</li> <li>Clinicopathological prognostic parameters for high risk and aggressiveness</li> </ol>	<ol> <li>Provides detailed histological subtyping of a PitNET based on the tumor cell lineage, cell type, and related characteristics</li> <li>Clearly differentiates adenohypophyseal, neurohypophyseal, and hypothalamic tumors</li> </ol>		
Classification—types and subtypes	<ol> <li>Corticotrophs—t-box PIT</li> <li>Gonadotrophs—SF1 &amp;/or GATA-2 + ER-α</li> <li>Somatotroph/lactotroph/thyrotroph-Pit-1</li> </ol>	<ol> <li>Adenohypophyseal         <ul> <li>PIT-1 lineage PitNETs</li> <li>TPIT-lineage PitNETs</li> <li>SF1-lineage PitNETs</li> <li>PitNETs with no distinct cell lineage</li> </ul> </li> <li>Pituitary blastoma</li> <li>Two types of craniopharyngioma</li> </ol>		
Addition from previous	1. Null cell tumor 2. PIT-1 positive plurihormonal tumor	<ol> <li>Mammosomotrophs</li> <li>Acidophil stem cell tumor</li> <li>Mature and immature plurihormonal PIT-1 lineage tumors</li> </ol>		
Removed from previous	Atypical adenoma	-		
Replaced terms	Pituitary adenoma	Pituitary neuroendocrine tumors		
	PIT-1 positive plurihormonal tumor	Mature and immature plurihormonal PIT-1 lineage tumors		
	Pituitary carcinoma	Metastatic PitNET		
	Traditional pituicytoma, spindle cell oncocytoma, granular cell tumor, sellar ependymoma	Oncocytic pituicytoma Granular cell pituicytoma, ependymal pituicytoma		
Limitations	Detailed histological subtyping not available	Two types of craniopharyngioma not well defined		
Proposal for next classification	The term—PitNET—for pituitary adenomas			

Table 1	Comparison of	4th and	5th Edition	of the WHC	) Classification	of Pituitary	/ Tumors
---------	---------------	---------	-------------	------------	------------------	--------------	----------

Abbreviations: ER-α, estrogen receptor-alpha; PitNET, pituitary neuroendocrine tumors; SF1, splicing transcription factor 1; TPIT, pituitary cell restricted factor; WHO, World Health Organization.

not poorly differentiated unlike the "carcinomas" where the differentiation is indiscriminate.<sup>18</sup> The 5th edition of the WHO Classification of Neuroendocrine Tumors has made significant advances in recognizing the progress made by the application of advanced tools to characterize tumors of the sellar region beyond the conventional hormonal activity that has been the basis for classification in past editions.<sup>19</sup> Tumors are now classified based on cell lineage as determined by expression of transcription factors, hormones, and other biomarkers. As with the other 5th edition WHO series, a specific tumor entity is now referred to as a tumor "type," whereas variants are considered "subtypes."<sup>8,19</sup>

# Current Controversies Related to the New Nomenclature

Despite of the fact that in the newer classification, approach and new descriptions for pituitary tumors have been put forward. The discrepancies of the newer nomenclature still exist. The introduction of the term PitNET, recommended by the International Pituitary Pathology Club, can incorporate the arbitrary malignant nature as seen in the subset of aggressive pituitary adenomas (PAs) that amounted to only 10% of the pituitary tumors and is nonresponsive to traditional treatment.<sup>17</sup> However, a group of endocrinologists who defy the new terminology as according to them it is misleading. It portrays PAs as harmful and cancerous when majority are not aggressive. Thus, this terminology might add new ambivalence to the origin of PAs and needless frustrations and apprehension among most of the patients diagnosed with benign PAs.<sup>20,21</sup>

In earlier classifications, null cell tumors were a diagnosis of exclusion, that is, when exhibiting no distinct transcription factor.<sup>22</sup> But now although being a member of adenohypophyseal cell lineage, and not expressing PIT-1 transcription factor,<sup>8,21,23</sup> they have been classified as a separate entity thereby disrupting the association between tumors of PIT-1 lineage and null cell tumors that further create confusion regarding the origin of null cell tumors. Another debatable point in the new classification is that the mammosomatotrophs were considered as those tumors arising from a common acidophilic progenitor cell with no distinct cell lineage and consecrating GH and

prolactin (PRL),<sup>24</sup> whereas now they have been classified under tumors expressing PIT-1 transcription factors that were usually originating from adenohypophyseal cell lineages.<sup>8,25</sup> This classification of mammosomatotroph in the newer classification is controversial.

# Utility of the Nomenclature from a Neurosurgeons Perspective

The new WHO classification of PitNET/PA has incorporated tremendous advances in the understanding of the cytogenesis and pathogenesis of pituitary tumors. However, due to the shortcomings of the technology used in the diagnosis of PitNET/PA and the limited understanding of the tumorigenesis of PitNET/PA, the application of this new classification system in clinical practices should be further assessed and verified.

Other than contributing to the follow-up strategy and postsurgical management of pituitary tumors, this classification does not provide any favorable information for the neurosurgeons in clinical practice and decision making, especially in determining the plan of action for the surgery.<sup>26</sup> Therefore, it is of utmost importance for neurosurgeons to exhibit a well-structured elaborate pituitary classification system for PitNET/PA that includes neuroimaging grading data or per-operation observation of invasiveness or the predictor of prognosis, as well as diagnosis made pathologically, thereby identifying the invasive nature of the tumor and clearing the way for neurosurgeons to opt on the treatment plans and follow-up strategies as well as postoperative ancillary treatment.<sup>27</sup>

### Conclusion

In summary, the prevalence of pituitary tumors has recently increased, but most patients are asymptomatic and do not need treatment. Although the revised new nomenclature has used advanced molecular technologies for classifying the tumors, it does not provide any extra edge to the neurosurgeons in clinical practice. Instead, it has made the management process of the patients more cumbersome that will lead to unnecessary anxiety among them which would further aggravate their clinical symptoms, and this will be detrimental for the neurosurgeons in providing them treatment. Hence, there is need of a more comprehensive, neuroradiological-based classification with more emphasis on the invasiveness of these tumors that would assist the neurosurgeons in planning the treatment strategy and managing patients of pituitary tumors.

### Recommendations

Pituitary tumors need a multidisciplinary approach for management and neurosurgeons are the first point of contact in such patients. There is need of an integrated classification of pituitary tumors amalgamating the clinical symptoms, genetic component, biochemical and radiological features along with pathological and molecular information. This will help in planning the surgery for these patients as well as postoperative chemotherapy and radiotherapy for preventing recurrences or treating the residual tumor. Hence, we recommend high level expert meetings of pioneers in the field of neurosurgery, endocrinology, molecular genetics, immunology, oncology, radiology, and others for developing an integrated classification system that can be beneficial in treating these patients.

Funding None.

Conflict of Interest None declared.

#### References

- 1 Asa SL, Perry A. (2020) Tumors of the Pituitary Gland. AFIP Atlas of Tumor and Non-Tumor Pathology. Arlington VA: ARP Press
- 2 Osamura RY, Kajiya H, Takei M, et al. Pathology of the human pituitary adenomas. Histochem Cell Biol 2008;130(03):495–507
- <sup>3</sup> Jentoft ME, Osamura RY, Kovacs K, Lloyd RV, Scheithauer BW. Transdifferentiation of pituitary thyrotrophs to lactothyrotrophs in primary hypothyroidism: case report. Virchows Arch 2012;461 (02):221–225
- 4 Melmed S. Pathogenesis of pituitary tumors. Nat Rev Endocrinol 2011;7(05):257–266
- <sup>5</sup> Mehta GU, Lonser RR. Management of hormone-secreting pituitary adenomas. Neuro-oncol 2017;19(06):762–773
- 6 Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). Clin Endocrinol (Oxf) 2010;72(03):377–382
- 7 Agustsson TT, Baldvinsdottir T, Jonasson JG, et al. The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. Eur J Endocrinol 2015;173(05):655–664
- 8 Asa SL, Mete O, Perry A, Osamura RY. Overview of the 2022 WHO classification of pituitary tumors. Endocr Pathol 2022;33(01):6–26
- 9 Neou M, Villa C, Armignacco R, et al. Pangenomic classification of pituitary neuroendocrine tumors. Cancer Cell 2020;37(01):123–134.e5
- 10 Lloyd RV, Kovacs K, Young WF. Pitutary tumours: Introduction. In: WHO Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. Chapter 1: Tumours of Pituitary; WHO: Lyon, France; 2004:10–13
- 11 Al-Shraim M, Asa SL. The 2004 World Health Organization classification of pituitary tumors: what is new? Acta Neuropathol 2006;111(01):1–7
- 12 Villa C, Vasiljevic A, Jaffrain-Rea ML, et al. A standardised diagnostic approach to pituitary neuroendocrine tumours (PitNETs): a European Pituitary Pathology Group (EPPG) proposal. Virchows Arch 2019;475(06):687–692
- 13 Nishioka H, Inoshita N. New WHO classification of pituitary adenomas (4th edition): assessment of pituitary transcription factors and the prognostic histological factors. Brain Tumor Pathol 2018;35(02):57–61
- 14 Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta Neuropathol 2017;134(04):521–535
- 15 Tiwari S, Pant I, Chaturvedi S. Pituitary tumors: changing paradigms in understanding, nomenclature and the newer basis of classification. Astrocyte 2018;4(04):240
- 16 Trouillas J, Jaffrain-Rea ML, Vasiljevic A, Raverot G, Roncaroli F, Villa C. How to classify pituitary neuroendocrine tumors (PitNET) s in 2020. Cancers (Basel) 2020;12(02):514
- 17 Asa SL, Casar-Borota O, Chanson P, et al; attendees of 14th Meeting of the International Pituitary Pathology Club, Annecy, France, November 2016. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): an International Pituitary Pathology Club proposal. Endocr Relat Cancer 2017;24(04):C5–C8

- 18 Ho KKY, Fleseriu M, Wass J, et al. A tale of pituitary adenomas: to NET or not to NET: pituitary Society position statement. Pituitary 2019;22(06):569–573
- 19 Rindi G, Klimstra DS, Abedi-Ardekani B, et al. 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 2018;31(12):1770–1786
- 20 Mete O, Kefeli M, Çalışkan S, Asa SL. GATA3 immunoreactivity expands the transcription factor profile of pituitary neuroendocrine tumors. Mod Pathol 2019;32(04):484–489
- 21 Punsoni M, Asa SL. Pituitary neuroendocrine tumor (PitNET). PathologyOutlines.com website. Accessed November 7, 2023 at: https:// www.pathologyoutlines.com/topic/CNSpituitaryendocrine.html
- 22 Nickel B, Semsarian C, Moynihan R, et al. Public perceptions of changing the terminology for low-risk thyroid cancer: a qualitative focus group study. BMJ Open 2019;9(02):e025820

- 23 Dai C, Kang J, Liu X, Yao Y, Wang H, Wang R. How to classify and define pituitary tumors: recent advances and current controversies. Front Endocrinol (Lausanne) 2021;12:604644
- 24 Mete O, Cintosun A, Pressman I, Asa SL. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. Mod Pathol 2018;31(06):900–909
- 25 Hong SW, Kim SH, Lim SH, et al. Clinical relevance of New World Health Organization classification system for pituitary adenomas: a validation study with 2-year experience. Front Oncol 2021; 11:739290
- 26 Kim J, Yoon SJ, Moon JH, et al. Clinical significance of radical surgery in the treatment of silent corticotroph adenoma. J Korean Neurosurg Soc 2019;62(01):114–122
- 27 Wan XY, Chen J, Wang JW, Liu YC, Shu K, Lei T. Overview of the 2022 WHO classification of pituitary adenomas/pituitary neuroendocrine tumors: clinical practices, controversies, and perspectives. Curr Med Sci 2022;42(06):1111–1118