




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

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## 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

- ▶ pituitary tumors
- ▶ PiTNETs
- ▶ WHO classification
- ▶ management
- ▶ pituitary adenomas

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## 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, adenohypophyseal, 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 subdivided 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. “Atypical” adenoma was eliminated from this classification.<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

**Table 1** Comparison of 4th and 5th Edition of the WHO Classification of Pituitary Tumors

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 style="list-style-type: none"> <li>1. Adenohypophyseal cell lineages for classification and subtypes determined by transcription factors</li> <li>2. Clinicopathological prognostic parameters for high risk and aggressiveness</li> </ol>	<ol style="list-style-type: none"> <li>1. Provides detailed histological subtyping of a PitNET based on the tumor cell lineage, cell type, and related characteristics</li> <li>2. Clearly differentiates adenohypophyseal, neurohypophyseal, and hypothalamic tumors</li> </ol>
Classification—types and subtypes	<ol style="list-style-type: none"> <li>1. Corticotrophs—t-box PIT</li> <li>2. Gonadotrophs—SF1 &amp;/or GATA-2 + ER-<math>\alpha</math></li> <li>3. Somatotroph/lactotroph/thyrotroph-Pit-1</li> </ol>	<ol style="list-style-type: none"> <li>1. Adenohypophyseal <ul style="list-style-type: none"> <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>2. Pituitary blastoma</li> <li>3. Two types of craniopharyngioma</li> </ol>
Addition from previous	<ol style="list-style-type: none"> <li>1. Null cell tumor</li> <li>2. PIT-1 positive plurihormonal tumor</li> </ol>	<ol style="list-style-type: none"> <li>1. Mammosomatotrophs</li> <li>2. Acidophil stem cell tumor</li> <li>3. 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	

Abbreviations: ER- $\alpha$ , 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.

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#### Conflict of Interest

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