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Perspective

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Pituitary adenoma or neuroendocrine tumour: the need for an integrated prognostic classification

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Abstract

In the 2022 fifth edition of the WHO Classification of Endocrine Tumours and of Central Nervous System Tumours, pituitary adenomas are reclassified as neuroendocrine tumours (NETs). This change confers an oncology label to neoplasms that are overwhelmingly benign. A comprehensive clinical classification schema is required to guide prognosis, therapy and outcomes for all patients with pituitary adenomas. Pituitary adenomas and NETs exhibit some morphological and ultrastructural similarities. However, unlike NETs, pituitary adenomas are highly prevalent, yet indolent and rarely become malignant. This Perspective presents the outcomes of an interdisciplinary international workshop that addressed the merit and clinical implications of the classification change of pituitary adenoma to NET. Many non-histological factors provide mechanistic insight and influence the prognosis and treatment of pituitary adenoma. We recommend the development of a comprehensive classification that integrates clinical, genetic, biochemical, radiological, pathological and molecular information for all anterior pituitary neoplasms.

Sections

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Introduction

Pituitary adenomas are common indolent neoplasms[1]. They can cause morbidity through excessive hormone production and local sellar growth and very rarely undergo malignant transformation. Pituitary adenomas are managed either conservatively or with drugs, surgery or irradiation, or through a combination of these modalities, depending on their type and behaviour. Pituitary adenomas are variably classified by function, size, invasiveness, phenotype and histology, all aimed to guide prognosis and therapy. More than half of adenomas that cause clinically important health issues do not require surgery[1]. Therefore, pituitary neoplasms that do not require surgery cannot be classified histologically. A comprehensive clinical classification schema that guides the prognosis, therapy and outcomes of all pituitary adenomas is not currently available.

The WHO Family of International Classifications includes a pathology-based system widely used for the classification of pituitary adenomas. The 2022 edition of the WHO Classification of Endocrine Tumours and of Central Nervous System Tumours reclassifies pituitary adenomas as neuroendocrine tumours (NETs)[2]. Although pituitary adenomas are overwhelmingly benign[1,3], both the International Classification of Diseases for Oncology (ICD-O) and International Classification of Diseases 11th Revision (ICD-11) grade NETs as malignant tumours, thereby categorizing all pituitary adenomas as malignant, which does not reflect how they behave nor how they are clinically managed. Owing to this perceived concern, the Pituitary Society convened an international multidisciplinary workshop to address the implementation, validity, merit and clinical implications of a pathology-based classification change on patient care.

This Perspective presents the outcomes of this workshop. We outline the principles of disease classification and criteria that should be considered when making changes to disease classification. We discuss the process undertaken during the current classification change of pituitary adenoma to NET. We briefly describe how the workshop was organized before highlighting relevant topics to the discussion, including pituitary adenoma biology, taxonomy, classification and clinical implications. Finally, we propose that an integrated, comprehensive classification be developed to guide the prognosis, therapy and outcomes for pituitary adenoma, by including clinical, genetic, biochemical, radiological, pathological and molecular information.

Disease classification

Classification of diseases, including the widely used ICD maintained by the WHO, frames the practice of medicine, providing a foundation for disease study as well as shaping and guiding the understanding of individual and societal implications of specific disease diagnoses[4].

Classification changes

Disease classifications are refined by advances in relevant health disciplines. Changes are usually implemented when sufficient evidence accumulates to alter disease criteria, when there is a change in diagnostic sensitivity or risk stratification, or with the discovery of novel mechanistic insights elucidating disease pathogenesis[5]. By altering inclusion boundaries, changes in disease classification can distort historical trends in disease prevalence and therapy outcomes. Furthermore, when such changes are proposed, consideration should be given as to whether they are based upon opinion or evidence as well as to whether academic, patient and financial conflicts of interest have been accounted for[5].

Process

The Pituitary Society has expressed concern regarding the process by which pituitary adenomas were reclassified as NETs[3,6–8]. As the process of implementing classification change demands rigorous evaluation, guiding principles have been developed for this purpose[9] (Box 1). Regrettably, in reviewing these principles, we considered that they were not followed for the reclassification of pituitary adenomas as NETs, including stakeholder consultation, prognostic utility, and consideration of benefits and harms. The trigger for the change in classification from pituitary adenoma to pituitary neuroendocrine tumour (PitNET) was an opinion piece published in 2017 (ref. 10) stating that pituitary adenomas exhibit a spectrum of behaviours that are not entirely benign, manifesting similarities to NETs in causing morbidity from mass effect and hormone excess syndromes. The authors contended that "pituitary hormone-producing cells are members of the family of neuroendocrine cells" to justify the proposal "that neoplasms of adenohypophysial cells be termed 'pituitary neuroendocrine tumors'". Notable in that opinion piece was the absence of a discussion on the histological distinction between neuroendocrine and endocrine cells and the inaccurate claim for these lesions that "a large proportion (40%) is invasive" (see later)[10]. This opinion piece foreshadowed that, "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 to be included in the next edition"[10]. The change from pituitary adenoma to PitNET was implemented in the 2022 WHO classification (fifth edition)[2] without consultation or academic discourse with endocrine and neurosurgical professional societies. We find it troubling that the

Box 1

Underlying principles justifying a change of disease classification

- Define the impetus driving the change in disease classification.
- Describe how the new proposed classification differs from the prior classification.
- Clarify whether the new proposed classification alters disease epidemiology, including incidence and prevalence.
- Demonstrate how the new proposed classification better predicts disease outcomes, including morbidity and mortality.
- Provide evidence that the new proposed classification is rigorously validated and reproducible by stakeholder communities.
- Demonstrate that the new proposed classification yields additive and meaningful benefit to patient care, including quality of life and clinical symptoms.
- Consider the potential for the new proposed classification to adversely affect patient welfare.
- Provide evidence that the benefit to patients in changing disease classification outweighs any potential harm.

These principles were originally developed and presented in ref. 9.

literature was seeded with the term 'PitNET' in more than 180 publications in the 5 years before being endorsed by the WHO and published in their 2022 classification[2].

Pituitary Neoplasm Nomenclature workshop

In response to these concerns, the Pituitary Society convened an international Pituitary Neoplasm Nomenclature (PANOMEN) workshop in 2021, inviting stakeholder societies representing developmental biology, pathology, neurosurgery and endocrinology: The Endocrine Society, European Society of Endocrinology, European Neuroendocrine Association, Growth Hormone Research Society, and International Society of Pituitary Surgeons[6]. The International Agency for Research on Cancer (IARC), an intergovernmental agency forming part of the WHO, was invited but unable to attend[6]. The workshop concluded that the term PitNET was not helpful in guiding prognosis and recommended that: first, the term 'adenoma' be retained; second, imaging grades be incorporated into the classification of pituitary neoplasms; third, patients be engaged to provide future input; and fourth, the workshop report be sent to the IARC of the WHO for consideration in preparing the classification.

The fifth edition of the WHO Classification of Endocrine Tumours and Central Nervous System Tumours published in 2022 (ref. 2) retains the use of adenoma along with NET in duality during transition, foreshadowing a move to solely NET terminology in a future edition. If so, this is a concerning development, signalling a move oblivious to the first PANOMEN workshop report stating that the NET terminology is confusing, risking social and health-care consternation[7]. Thus, a pathological classification change was implemented without due consideration given to clinical consequences.

Therefore, the Pituitary Society convened a second international workshop (PANOMEN 2), resulting in the writing of this Perspective (Box 2). To ascertain whether a more comprehensive classification is required, the workshop reviewed the validity, merit, adequacy and clinical consequence of the new 2022 classification for patients with pituitary adenomas. As with the first workshop in 2021, the second workshop, held in late 2022, again invited major international stakeholder societies and included a patient organization (see later). The workshop programme covered evidence-based biology, taxonomy and clinical consequences, and examined the strengths and weaknesses of proposed pituitary adenoma classifications. The basic principles of an integrated classification of anterior pituitary neoplasms that can meaningfully assist management and prognostication are proposed here.

Box 2

Guiding principles for the PANOMEN 2 workshop

The principles guiding the Pituitary Neoplasm Nomenclature (PANOMEN) 2 workshop organization were stakeholder inclusiveness, transparency, unbiased speaker selection, open discussion and open voting-determined outcomes. The Pituitary Society invited national and international professional organizations to appoint representatives to participate in the workshop: Endocrine Society (U.K., L.R.), American Association of Clinical Endocrinology (D.E., K.Y.), European Society of Endocrinology (J.C., O.C-B.), European Neuroendocrine Association (G.R., M.Z.), International Society of Pituitary Surgeons (A.L., M.A.), The US and Canadian Academy of Pathology (M.B.S.L), and the Acromegaly Community (J.S.). Speakers comprised opinion leaders in pituitary medicine, epidemiology, developmental biology, cell and molecular biology, pathology, neurosurgery, endocrinology, and oncology. The workshop structure (similar to previous Pituitary Society consensus meetings[51]) included breakout discussion groups that returned summary reports for consensus drafting in an open forum, from which an integrated written draft was produced and then circulated for additional comments, revision and, ultimately, final approval. The PANOMEN 2 workshop was planned by K.H. and S.M. serving as Co-Chairs and P.C., M.G., U.K., M.R., and J.W. serving as Steering Committee Members. A.B. and L.E. were invited as pathology experts. M.B.S.L and O C-B participated in the workshop but are not authors of the manuscript (see acknowledgements).

Biology

The clinical epidemiology of pituitary adenomas and NETs are summarized and compared in this section.

Epidemiology of pituitary adenomas

Pituitary adenomas are common, occurring in about 10% of the population as reported from autopsy and imaging surveys[1] (Fig. 1). However, clinically important health issues attributable to pituitary adenomas only occur in about 70–100 out of every 100,000 persons[11,12], with an annual incidence of 1–5 cases per 100,000 people[13]. Among these, two-thirds are associated with excessive hormone secretion syndromes[1]. Fewer than 50% of diagnosed pituitary adenomas require surgical treatment and, of these, only 10% are locally invasive[1,14,15]. Pituitary microadenomas rarely increase in size over time[16–18] and are overwhelmingly diagnosed as small lesions localized to the pituitary sella; they are brought to attention owing to symptoms of hormone excess for secreting adenomas and/or mass effects for secreting or non-secreting adenomas. Although a small subset of pituitary adenomas behaves aggressively, showing resistance to treatment and multiple recurrences[19,20], malignancy is an exceptionally rare event, representing <0.1% of pituitary adenomas that come to clinical attention. Importantly, primary pituitary neoplasms are not malignant at the time of diagnosis and the majority (99.9%) are harmless and remain undetected during life[1], refuting the claim that "a large proportion (40%) is invasive"[10]. In fact, the main concern with the invasiveness of these lesions is not whether or not the mass is malignant but rather the risk of residual tissue after surgery, thereby increasing the risk of persistent hormone hypersecretion or of persistent mass growth[1].

Epidemiology of NETs

NETs arise from endocrine cells in the gut, pancreatic islets, lung, skin, adrenal medulla, thymus and neural tissues. Epidemiology studies report an annual NET incidence of up to 8.8 cases per 100,000 people per year[21,22]. Variability has been reported in growth and malignant potential within and between NETs arising from different tissues. Pulmonary NETs are the most frequent, followed by those of the small intestine[21]. Small intestinal NETs have an autopsy prevalence of 0.5% and a clinical incidence of 5.8 cases per 100,000 people per year[23]. By contrast, pituitary adenomas have a similar clinical incidence (see earlier text) but a striking 20-fold higher autopsy prevalence than

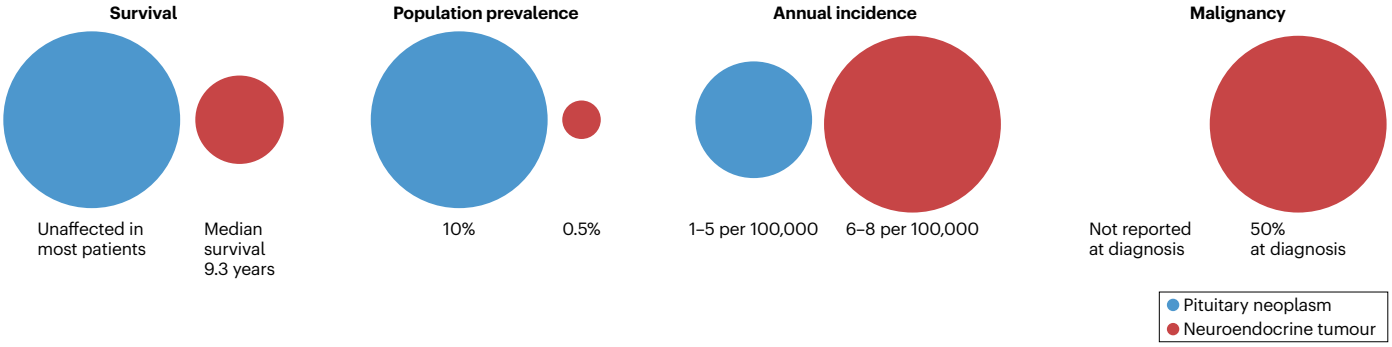

Fig. 1 | Comparing the epidemiology of pituitary neoplasms and neuroendocrine tumours. Schematic representation contrasting the population prevalence, annual incidence per 100,000 people, percentage of malignancy at the time of diagnosis, and survival in patients with pituitary neoplasms and neuroendocrine tumours.

NETs[1,24], indicating the indolent nature of pituitary adenomas. Even though many NETs are indolent, up to 50% are metastatic at the time of diagnosis[25], in marked contrast to primary pituitary neoplasms, which are not malignant when diagnosed. Appendiceal NETs have a lower metastatic potential than NETs arising from other tissues. Nevertheless, the 5-year survival rate for invasive appendiceal NETs with metastatic disease is <28%[26]. Thus, NETs demonstrate a striking heterogeneity not seen with pituitary adenomas. The median survival for patients with NETs is 9.3 years[27], whereas survival for patients with pituitary adenomas is rarely affected[1].

In summary, based on these reports, the workshop concluded that the epidemiology of pituitary adenomas differs from that of NETs. Pituitary adenomas are more prevalent than NETs, highly indolent and, unlike NETs, have little propensity for malignant transformation.

Taxonomy

Development

During embryonic development, the anterior pituitary gland is derived from oral ectoderm, driven by a sequentially timed cascade of intrinsic and extrinsic signals, mediated by lineage-specific transcription factors. These signals lead to highly differentiated polypeptide hormone-expressing cell types, producing adrenocorticotropic hormone (ACTH), growth hormone, prolactin, thyroid-stimulating hormone, or follicle-stimulating hormone and luteinizing hormone[1]. By contrast, the foregut, from which the small intestine, pancreas and gastrointestinal neuroendocrine cells are derived, is endodermal in origin. During embryonic development, transcription factors promote differentiation of the small intestine into three secretory lineages: goblet cells, Paneth cells and enteroendocrine cells[28]. Neurogenin 3 and NeuroD promote cellular differentiation into enteroendocrine and endocrine pancreas cells[29,30]. NeuroD also regulates various aspects of pituitary gland development[31]. Although many facets of neuroendocrine organ development differ from that of the anterior pituitary gland, differentiation of endoderm-derived and ectoderm-derived progenitor cells to endocrine cells is mediated by some common transcription factors[32,33].

Histological determinants of endocrine tumours and NETs

From a histological perspective, the proposed designation of pituitary adenomas as NETs is based on some common secretory mechanisms and expression of histological determinants considered to be neuroendocrine as distinct from markers of endocrine expression. Morphological, ultrastructural and molecular similarities exist between pituitary adenomas and NETs[34]. Pituitary cells display some neuroendocrine markers and neuroendocrine secretory machinery. In addition, similar to some other endocrine tissues, such as the parathyroid gland[35], pituitary adenomas and NETs store their hormone products in secretory granules and might express common cell surface proteins. Histological markers expressed by both pituitary adenomas and NETs include chromogranin A, synaptophysin, somatostatin receptors and insulinoma-associated protein 1 (INSM1)[36]. Except for INSM1, these markers lack neuroendocrine specificity as they can be expressed in other endocrine tumours, including non-neuroendocrine tumours such as follicular thyroid and adrenocortical tumours[37–39] and parafollicular C cells. However, they are not expressed in the normal adrenal cortex. Differentiation drivers, extrinsic stimuli and developmental biology differ among tissues that express neuroendocrine markers, yet it is unclear how developmental factors drive differentiated function and distinctive behaviour among endocrine and neuroendocrine tissues.

Classification

WHO pathological classification

The new WHO pathology-based PitNET nomenclature does not further guide prognosis, influence treatment options or determine outcomes. Thus, we consider that a name change in the pathological classification of pituitary adenoma to PitNET does not elucidate mechanistic insight or reflect the indolent biology and protracted natural history of the overwhelming majority of pituitary adenomas[6,7]. NETs are graded histologically by established proliferation markers (Ki67 or mitotic index) that correlate with growth, invasion and prognosis. Neuroendocrine carcinomas are identified by de-differentiation (aided by p53 or Rb expression). However, whether these markers correlate with pituitary adenoma behaviour has not been established and the 2022 WHO classification makes no recommendation on histological grading of PitNETs[2]. Although the new WHO classification continues to list some pituitary adenoma types (for example, sparsely granulated somatotroph adenomas, lactotroph adenomas in men, Crooke cell adenomas, silent corticotroph adenomas and immature plurihormonal Pit1-positive adenomas) as being potentially more aggressive than other types, the prognostic behaviour of these adenomas awaits prospective, controlled evaluation.

Overall, substituting the nomenclature of pituitary adenomas for NETs does not determine or influence prognosis. While reclassification of pituitary adenomas as NETs might increase awareness of a small minority of high-risk neoplasms that require increased surveillance, these cannot be identified by changing a name. Notably, the 2022 WHO pathological classification of pituitary adenomas as NETs, in particular the applied ICD-O and ICD-11 coding systems, places pituitary neoplasms in an oncology disease category that carries important health system implications for patient care (see later).

Clinicopathological classification

A pure pathological classification is limited to information derived from surgically resected tissue. Thus, pathological classification does not consider the majority of presumed pituitary adenomas that do not undergo surgical resection and omits vital radiological and clinical information. A clinicopathological classification has been developed for pituitary adenomas, combining imaging characteristics and histology in an attempt to integrate imaging invasion and proliferation indices[40]. The Knosp radiological classification characterizes invasiveness based on whether the lesion is confined within the sella or encroaches upon or extends beyond the cavernous and/or sphenoid sinus[41]. Growth activity is categorized by the absence or presence of histological markers of cell proliferation. Taken together, the risk of post-surgical adenoma recurrence correlates with the extent of cavernous sinus invasion, with the risk being greater in adenomas with higher proliferative activity than in those with lower activity[42–44]. Pituitary adenomas with high proliferative activity that extend into the cavernous sinus exhibit up to five-times greater likelihood of recurrence and require multiple treatment modalities compared with those confined to the sella with low proliferative activity[43].

Thus, this clinicopathological system, combining imaging and histology, might predict prognosis. However, a weakness of this approach is the inability to specifically identify individual neoplasms that will progress, recur or ultimately metastasize.

Mechanistic, genetic and secretory information also influences the prognosis of pituitary adenomas. Novel molecular markers that could predict outcomes include *GNAS* mutations in somatotroph adenomas[45,46] and *USP8* mutations[47] and *ATRX* mutations in corticotroph adenomas[48]. Familial and syndromic forms of pituitary adenomas also exhibit unique disease phenotypes, prognosis and treatment outcomes[1]. Knowledge of these genomic, genetic and secretory characteristics is not included in the current PitNET classification.

Grading and staging

Although grading and tumour, node, metastasis (TNM) staging provide prognostic value for NETs[26,49], the WHO classification does not grade or stage pituitary adenomas. As the majority of pituitary adenomas are indolent and very rarely metastasize, a NET-based TNM size and invasion classification system is unlikely to be applicable to pituitary adenomas. For example, without knowledge of clinical biology, at first glance, the prognosis for giant invasive prolactinomas would be considered poor. However, in most individuals, macroprolactinomas and giant prolactinomas shrink markedly with prolactin secretion control in response to dopamine agonist therapy, without the need for chemotherapy, surgery or histological confirmation[1,50]. For ACTH-secreting adenomas, patient prognosis is influenced by the extent and duration of hypercortisolism rather than by adenoma size[51]. Even for non-secreting pituitary adenomas, histological grading has not been shown to prospectively and independently determine mortality[52].

No comprehensive validated staging or grading system exists for pituitary adenomas, and the grading and staging system for NETs cannot be meaningfully applied to pituitary adenomas. Owing to major differences in the distribution of tumour stage and in prognostication between NET and pituitary adenoma types, the NET grading and staging system is inappropriate for pituitary adenomas. Accordingly, development of a grading and staging system is required for pituitary adenomas, given the influence that such a system could have on pathological classification.

Clinical implications

For a disease classification name change, consideration of the patient perspective and the potential health-care consequences are particularly important. Selection of accurate nomenclature to describe a pituitary lesion is especially important for patients and caregivers as these labels influence patient decision-making[53] and even provider recommendations. As the term ‘tumour’ is often associated by patients with a malignancy[54], we propose that the classification change of pituitary adenoma to NET could lead to overtreatment, increased patient anxiety, difficulties with health and life insurance coverage, and other unanticipated adverse experiences[6]. Oncology designation might result in unforeseen subsequent management consequences in the health system and in the electronic medical record. To address the validity of these concerns, the workshop invited participation from a large global patient organization and oncology health-care experts outside the field of pituitary medicine.

The patient perspective

The patient perspective was sought using a structured questionnaire administered by the Acromegaly Community, a global support group for patients and caretakers, to gauge patient sentiment regarding the name change with respect to cancer risk, anxiety, appropriate treatment, health-care provision and insurability. The Acromegaly Community representative at the workshop reported, based on the administered patient survey, that the majority agreed or expressed uncertainty that the name change would lead to more intensive and unnecessary laboratory and/or imaging investigations, and would thus adversely affect their well-being (J.S., unpublished work). The survey is currently being prepared for publication. The Acromegaly Community representative also expressed concern that an internet search of leading academic institutions in the USA emphasized the malignant potential of NETs, with one describing NETs as “cancers that begin in specialized cells”.

Health system implications

Cancers are heterogeneous lesions comprising a spectrum of atypical, low-grade and high-risk neoplasms, the treatments of which need to be tailored appropriately. For thyroid, prostate, breast and lung cancer, a growing shift in awareness has occurred towards recognition of the deleterious effects of overtreatment. Overdiagnosis is a concerning negative consequence of cancer screening that can lead to overtreatment[55]; up to 24% of cancers are estimated to be overdiagnosed[56]. For breast neoplasms, ductal carcinoma in situ is a common indolent lesion of low malignant potential[57] and the term ‘indolent lesion of epithelial origin’ has been introduced to rebrand ductal carcinoma in situ and de-escalate overdiagnosis and overtreatment[58]. This change is highly pertinent and in marked contrast to the blanket rebranding of pituitary adenomas as NETs. Unlike breast neoplasms, no histological markers are known that can independently predict aggressive or malignant

behaviour in pituitary adenomas, thereby enhancing the risk of escalating overdiagnosis and treatment as cancers.

Lessons can also be learned from the evolution of prostate cancer classification and the difficulty in downgrading terminology to reduce harm from overtreatment[59,60]. With increasing evidence that language and terminology shape psychosocial behaviour for both patients and health-care providers, concern has been raised in the PANOMEN workshops that the oncological connotations associated with the use of the term NET risk overdiagnosis and overtreatment of pituitary adenomas[6].

If pituitary adenomas are reclassified as NETs, there is potential that patients or their primary care physicians might perceive their pituitary adenoma as an aggressive cancer, even for small non-functioning neoplasms. As a consequence, patients or their physicians might be unnecessarily alarmed and seek care from oncologists rather than from pituitary experts, potentially leading to unnecessary testing, unnecessary medication and surgery, and adverse implications on health and life insurance policies.

Scope

A major gap in pathological or clinicopathological classification systems is the exclusion of pituitary adenomas that come to clinical attention after incidental diagnosis but do not require surgery and therefore never yield a pathological diagnosis. These neoplasms are usually small, non-functioning and slow growing[16,18]. They are not subjected to surgical resection unless there is evidence of rapid growth, invasion or potential compression of critical adjacent structures such as the optic chiasm. The histological characterization of pituitary adenomas, especially of non-functioning pituitary adenomas, is therefore subject to bias because of the selection of large and actively growing tumours. We propose that the 2022 WHO classification thus overstates the biological aggressiveness of adenomas that undergo surgery. An additional weakness of the 2022 WHO classification is that it does not consider predictive factors that notably affect clinical outcomes, such as hormone secretory function, genetics and genomics, in addition to histopathological features. For example, pituitary adenoma hypofunction and hyperfunction both influence mortality[1].

Hereditary disorders account for a range of distinct syndromes causing acromegaly, prolactinomas, Cushing disease and non-functioning adenomas[1]. Germline mutations underlying these disorders have provided mechanistic insight and informed prognosis without requiring histological analysis[61]. Gene mutations that elucidate mechanistic and prognostic information[45,47,48,62] are yet to be integrated into a pituitary adenoma classification system. Thus, many important transcending issues exist concerning pituitary adenomas that go beyond histology, taxonomy and nomenclature.

Clinical classification

A compelling need exists for an overarching, comprehensive clinical classification schema that guides prognosis, therapy and outcomes for all pituitary adenomas. The wealth of clinically relevant evidence-based information across histological, genetic, genomic, transcriptomic and secretory function should be consolidated into such a schema, with key factors graded in accordance with risk. We propose that a schema for pituitary adenomas should apply to two cohorts. First, unresected anterior pituitary adenomas should be categorized by clinical phenotype, considering factors including age, sex, phenotype, biochemistry, secretory status, imaging characteristics, mass effect and genetics, with each graded by a numerical score. Second, surgically resected anterior pituitary adenomas should be categorized by lineage, integrating clinical, radiological, pathological, secretory and molecular information, with each graded by a numerical score.

Summary

Pituitary adenomas have been newly classified as PitNETs. The absence of external consultation preceding this change has raised concerns among clinicians and patient stakeholders. The authors of this Perspective convened an interdisciplinary international workshop to address the merit of a pathological classification change of pituitary adenomas to NETs by reviewing developmental and molecular biology, histology, epidemiology and clinical implications. Despite some morphological, ultrastructural and molecular similarities between pituitary adenomas and NETs, their embryonic origins are different. Unlike neuroendocrine neoplasms, pituitary adenomas are highly prevalent and typically indolent and rarely metastasize or de-differentiate. We propose that the classification change to NET does not advance mechanistic insight, treatment or prognosis but confers a misleading oncology label, potentially leading to overtreatment. A shortcoming of a pathology-based classification system is the omission of pituitary adenomas from patients who do not undergo surgery. These include those that are diagnosed clinically and controlled by drug therapy, therefore they do not require surgery or a tissue diagnosis. They also include adenomas in patients who decline surgery for personal reasons or owing to co-existing morbidities. Many factors independent of histopathology yield mechanistic insight into the biology of pituitary adenomas and influence their prognosis and treatment. The present classification system contains a void for guiding the prognosis and management of pituitary adenomas.

Conclusions

We propose that the pathological classification change of pituitary adenomas to NETs does not advance the management of pituitary adenomas. As a pathology-based classification system can only apply to resected lesions, a need exists for a comprehensive classification system that also includes the majority of pituitary adenomas that do not require surgery.

PANOMEN 2 recommends the development of a comprehensive clinical classification comprising attributes that integrate clinical, genetic, biochemical, radiological, pathological and molecular information for all pituitary adenomas. This classification model will be based on a consolidated grading of determinants derived from the quantification of appropriate evidence-derived biomarkers.

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