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Pituitary Neuroendocrine Tumors: A Narrative Review of Epidemiology, Classification, Pathogenesis, Diagnosis, and Management

Tumor Neuroendokrin Hipofisis: Tinjauan Naratif mengenai Epidemiologi, Klasifikasi, Patogenesis, Diagnosis, dan Tatalaksana

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Abstract

This narrative review aimed to summarize current evidence on the epidemiology, classification, pathogenesis, clinical manifestations, diagnosis, histopathology, management, and prognosis of PitNETs. Literature searches were conducted through PubMed/MEDLINE and Google Scholar using combinations of terms related to PitNETs, pituitary adenomas, epidemiology, classification, genetic and epigenetic mechanisms, clinical manifestations, diagnosis, MRI, histopathology, treatment, recurrence, and prognosis. The reviewed evidence indicates that PitNETs range from incidental and clinically nonfunctioning tumors to hormone-secreting tumors associated with distinct endocrine syndromes. Recent classification systems emphasize transcription factor-based lineage determination, particularly PIT1, TPIT, and SF1, reflecting the biological heterogeneity of these tumors. Genetic alterations, epigenetic regulation, intracellular signaling abnormalities, mitochondrial dysfunction, and oxidative stress contribute to tumor development and behavior. Diagnosis requires integration of hormonal evaluation, pituitary magnetic resonance imaging, visual assessment when indicated, and histopathological examination. Management is individualized according to hormonal activity, tumor size, anatomical extension, visual or neurological involvement, and residual or recurrent disease. Long-term follow-up remains important because hormonal abnormalities, hypopituitarism, tumor recurrence, treatment-related complications, and impaired quality of life may persist despite treatment.

INTRODUCTION

Pituitary neuroendocrine tumors (PitNETs), historically referred to as pituitary adenomas, are predominantly slow-growing tumors arising from adenohypophyseal cells. Their clinical significance varies according to hormonal activity, tumor size, local extension, and effects on pituitary or visual function. The increasing use of magnetic resonance imaging (MRI) has contributed to the detection of previously unrecognized pituitary lesions, including incidental tumors (Daly & Beckers, 2020). Population-based studies have reported an incidence of approximately 3.9–7.4 cases per 100,000 persons per year and a prevalence of 76–116 cases per 100,000 population, although estimates vary according to diagnostic criteria and population characteristics (Day *et al.*, 2016). Pituitary

tumors therefore represent an important cause of endocrine dysfunction and sellar mass-related neurological or visual manifestations (Chen *et al.*, 2021).

The classification of pituitary tumors has evolved with advances in histopathology and molecular biology. The fifth edition of the World Health Organization (WHO) classification emphasizes the neuroendocrine nature of anterior pituitary tumors and incorporates transcription factors, hormone expression, and cellular characteristics to define tumor lineages and subtypes (Asa *et al.*, 2022). This framework emphasizes PIT1-, TPIT-, and SF1-lineage differentiation and may reclassify tumors previously considered null cell or hormonally inactive, providing closer correlation with tumor biology (Nasi Kordhishti *et al.*, 2025). Nevertheless, hormonal activity and tumor size remain clinically important because they influence presentation, diagnosis, treatment selection, and follow-up (Banskota & Adamson, 2021).

The pathogenesis of PitNETs is heterogeneous and involves genetic, epigenetic, and intracellular signaling abnormalities. Somatic alterations in intracellular signaling, including *GNAS* alterations in somatotroph tumors, have been implicated in tumor development (Tatsi & Stratakis, 2019). Germline abnormalities involving *MEN1* and *AIP* are associated with familial and syndromic pituitary tumors, particularly in patients with early-onset disease or a relevant family history (Van den Broek *et al.*, 2019). Epigenetic changes, mitochondrial dysfunction, and oxidative stress may also contribute to tumor development and progression, although their roles vary among subtypes (Chang *et al.*, 2021; Wu *et al.*, 2024). These findings support a multifactorial basis for PitNET development (Zhou *et al.*, 2023).

Clinically, PitNETs range from incidental lesions to endocrine, neurological, and visual disorders. Functioning tumors may cause hyperprolactinemia, acromegaly, or Cushing disease, whereas clinically nonfunctioning tumors commonly present with headache, visual disturbances, hypopituitarism, or mass effect (Vieira *et al.*, 2016). Diagnosis integrates pituitary hormone assessment and dedicated pituitary MRI, with ophthalmological evaluation when the optic apparatus is involved or at risk (Fleseriu *et al.*, 2025). Management is individualized according to tumor subtype, hormonal activity, anatomical extension, visual or neurological compromise, and residual or recurrent disease, using medical therapy, surgery, or radiotherapy as appropriate (Banskota & Adamson, 2021).

Despite these advances, evidence linking the evolving WHO classification with molecular characteristics, diagnostic findings, and clinical management remains fragmented across different study settings (Asa *et al.*, 2022; Chang *et al.*, 2021). Recent developments in molecular biology, histopathology, imaging, and treatment further highlight the need for an updated synthesis that connects tumor lineage and biology with clinical decision-making and outcomes (Nasi Kordhishti *et al.*, 2025; Fleseriu *et al.*, 2025). This narrative review therefore integrates current evidence on the epidemiology, classification, pathogenesis, clinical manifestations, diagnosis, histopathology, management, and prognosis of PitNETs, with particular emphasis on the relationship between contemporary classification, molecular mechanisms, and clinical care.

METHODS

This article was prepared as a narrative review of pituitary neuroendocrine tumors (PitNETs), historically referred to as pituitary adenomas, focusing on epidemiology, classification, pathogenesis, clinical manifestations, diagnosis, histopathology, management, and prognosis. The literature search was conducted through

PubMed/MEDLINE and Google Scholar for publications from January 2019 to July 2026, with the final search performed in July 2026. Search terms included PitNETs, pituitary adenomas, epidemiology, classification, genetic and epigenetic mechanisms, clinical manifestations, diagnosis, magnetic resonance imaging (MRI), histopathology, treatment, recurrence, and prognosis. Publications in English and Indonesian were included, while older studies were retained when providing foundational evidence.

Eligible publications included original studies, observational and epidemiological studies, systematic reviews, meta-analyses, clinical reviews, consensus statements, guidelines, and relevant reference books that addressed at least one predefined review domain. Studies involving other sellar or endocrine tumors without specific relevance to PitNETs, duplicate publications, and studies lacking sufficient clinical, pathological, epidemiological, molecular, or therapeutic information were excluded. Greater consideration was given to recent guidelines, consensus statements, systematic reviews, meta-analyses, and clinically relevant primary studies.

Retrieved records were screened by title and abstract, followed by full-text assessment according to the inclusion and exclusion criteria. Reference lists of relevant reviews, guidelines, and key studies were also examined to identify additional eligible publications. For Google Scholar, the same core concepts and keywords were used, and the first 100 results ranked by relevance for each search strategy were screened. Duplicate records were removed before final selection.

The selected literature was organized into epidemiology and classification, molecular pathogenesis, clinical manifestations and diagnostic evaluation, histopathology, management, and clinical outcomes including prognosis. Differential diagnosis was considered within the diagnostic domain. Findings were compared according to study design, population, PitNET subtype, diagnostic or pathological criteria, treatment modality, follow-up, and outcomes. Higher-level evidence was used to contextualize findings from primary studies, and the available evidence was synthesized narratively by identifying consistent findings, differences between studies, and areas of uncertainty.

RESULTS AND DISCUSSION

Results

The reviewed literature identified five major domains relevant to pituitary neuroendocrine tumors (PitNETs): epidemiology and classification, molecular pathogenesis, clinical manifestations, diagnosis and histopathology, and management and clinical outcomes. Epidemiological studies have shown that pituitary tumors are relatively common intracranial neoplasms, with reported incidence and prevalence varying according to the population and diagnostic methods used (Daly & Beckers, 2020). Population-based data have also demonstrated differences in patient characteristics, tumor distribution, and survival according to age, sex, and tumor subtype (Chen *et al.*, 2021). Recent pathological literature has further shifted the classification of these tumors from the traditional concept of pituitary adenomas toward PitNETs, with increasing emphasis on lineage-defining transcription factors and tumor cell differentiation (Asa *et al.*, 2022).

Molecular studies indicate that PitNET development involves heterogeneous genetic and epigenetic alterations rather than a single pathogenic mechanism. Somatic alterations in intracellular signaling pathways, including *GNAS*-related abnormalities, have been particularly associated with selected functioning tumors, whereas germline abnormalities involving genes such as *MEN1* and *AIP* contribute to familial or syndromic

forms of pituitary tumors (Tatsi & Stratakis, 2019). Genetic analysis may therefore provide clinically relevant information in selected patients, particularly those with early-onset disease, familial aggregation, or features suggestive of an inherited syndrome (Van den Broek *et al.*, 2019). In addition to genetic alterations, epigenetic regulation, microRNA abnormalities, mitochondrial dysfunction, and oxidative stress have been implicated in PitNET biology and may contribute to tumor growth, hormone secretion, and changes in the tumor microenvironment (Chang *et al.*, 2021). Recent evidence further supports the involvement of mitochondrial abnormalities and oxidative stress in PitNET development, although the clinical significance of these mechanisms remains dependent on tumor subtype and biological context (Wu *et al.*, 2024).

Clinical studies demonstrated that the presentation of PitNETs varies substantially according to hormonal activity, tumor size, and local extension. Functioning tumors may present with characteristic endocrine syndromes such as hyperprolactinemia, acromegaly, or Cushing disease, whereas clinically nonfunctioning tumors are frequently recognized because of mass effect, visual disturbance, headache, or pituitary hormone deficiencies (Vieira *et al.*, 2016). Nonfunctioning tumors may also produce clinically important hypopituitarism, including secondary hypothyroidism and other pituitary hormone deficiencies, particularly when the tumor is large or compressive (Cahyanur *et al.*, 2018). The available literature also indicates that clinical behavior differs according to sex, age, and tumor characteristics, with longitudinal studies demonstrating differences in growth patterns among clinically nonfunctioning PitNETs (Park *et al.*, 2024). These findings support the need to interpret clinical manifestations in relation to both endocrine activity and anatomical tumor characteristics.

Diagnostic studies consistently emphasized the combination of endocrine assessment, ophthalmological evaluation, neuroimaging, and pathological examination. Biochemical evaluation is directed toward identifying hormone hypersecretion and assessing anterior pituitary function, while dynamic endocrine testing may be required when basal hormone measurements are insufficient to establish the diagnosis of specific hormonal disorders (Lewis *et al.*, 2023). Dedicated pituitary MRI is the preferred imaging modality for evaluating sellar and suprasellar lesions, including assessment of tumor size, extension, relationship to the optic apparatus, and cavernous sinus involvement (Fleseriu *et al.*, 2025). Histopathological classification has subsequently become increasingly dependent on transcription factor expression, particularly PIT1, TPIT, and SF1, together with hormone expression and other cellular characteristics (Asa *et al.*, 2022). Radiological and pathological assessments therefore provide complementary information, with radiological invasion and pathological characteristics contributing to the evaluation of tumor behavior and prognosis (Serioli *et al.*, 2019).

Treatment outcomes differed according to hormonal subtype, tumor extension, residual disease, and recurrence risk. Medical therapy remains an important treatment modality for selected functioning PitNETs, while transsphenoidal surgery represents the principal surgical treatment for many tumors with visual compromise, mass effect, or other surgical indications (Banskota & Adamson, 2021). Studies of clinically nonfunctioning tumors have reported that transsphenoidal surgery can provide effective tumor control and improvement of mass-effect-related symptoms, although residual tumor and postoperative endocrine dysfunction remain relevant considerations (Choo *et al.*, 2022). For recurrent, residual, or selected unresectable tumors, radiotherapy or radiosurgery may be considered according to tumor location and its relationship with critical structures, particularly the

optic apparatus (Hefner & Cooper, 2025). Long-term outcomes also indicate that recurrence, persistent hypopituitarism, quality-of-life impairment, and mortality may remain clinically relevant even in tumors with relatively indolent growth (Castle-Kirszbaum *et al.*, 2024). These findings emphasize that clinical outcomes should be evaluated beyond tumor size alone and should include endocrine control, visual function, tumor control, treatment-related complications, and long-term quality of life (Bioletto *et al.*, 2024).

Table 1. Selected Studies Relevant to Epidemiology, Classification, Pathogenesis, Diagnosis, and Management of Pituitary Neuroendocrine Tumors

Author, year	Study design	Population/sample	Main focus	Main finding
Daly & Beckers, 2020	Epidemiological review	Literature on pituitary adenomas	Incidence and prevalence	Pituitary adenomas have a relatively high prevalence, although reported epidemiological estimates vary according to diagnostic methods and population characteristics.
Chen *et al.*, 2021	Population-based observational study	Patients with primary pituitary tumors in the SEER database	Epidemiology and survival	Demonstrated differences in demographic characteristics and survival among patients with primary pituitary tumors according to clinical and tumor-related characteristics.
Asa *et al.*, 2022	Pathological review	Literature on pituitary tumors	WHO 2022 classification	The 2022 WHO classification emphasizes the term PitNET and incorporates transcription factors and lineage differentiation into tumor classification.

Nasi Kordhishti *et al.*, 2025	Comparative clinicopathological study	921 pituitary adenomas/PitNETs	Transcription factor-based classification	Comparison across WHO classifications demonstrated the clinical implications of transcription factor-based classification and reclassification of some previously defined tumor categories.
Tatsi & Stratakis, 2019	Genetic review	Literature on pituitary adenoma genetics	Genetic mechanisms	Pituitary tumors involve diverse genetic alterations, including abnormalities affecting signaling pathways and genes associated with familial disease.
Van den Broek *et al.*, 2019	Systematic review	Patients with pituitary adenomas and genetic evaluation	Clinical relevance of genetic testing	Genetic analysis may be particularly relevant in patients with familial disease, young age at presentation, or features suggestive of hereditary pituitary tumor syndromes.
Chang *et al.*, 2021	Molecular review	Literature on genetic and epigenetic mechanisms	Genetic and epigenetic pathogenesis	Genetic alterations, epigenetic regulation, and microRNA abnormalities contribute to the development and

				biological behavior of pituitary adenomas.
Wu *et al.*, 2024	Molecular review	Literature on mitochondrial mechanisms	Mitochondrial dysfunction	Mitochondrial genetic and functional abnormalities are implicated in pituitary adenoma pathogenesis and may represent potential therapeutic targets.
Vieira *et al.*, 2016	Clinical review	Literature on clinically nonfunctioning pituitary adenomas	Diagnosis and treatment	Clinical assessment should integrate endocrine evaluation, imaging, visual assessment, and treatment selection according to tumor characteristics.
Fleseriu *et al.*, 2025	International consensus guideline	Evidence on pituitary incidentalomas	Diagnostic evaluation and follow-up	Dedicated pituitary MRI, endocrine assessment, visual evaluation when indicated, and individualized surveillance or surgical management are recommended.
Serioli *et al.*, 2019	Systematic literature review	Studies of pituitary adenoma invasiveness	Radiological and pathological invasiveness	Tumor invasiveness is influenced by anatomical, radiological, and histological characteristics

				and cannot be assessed using a single parameter.
Choo *et al.*, 2022	Retrospective surgical study	Patients with nonfunctioning pituitary adenoma	Transsphenoidal surgery	Transsphenoidal surgery provided relevant clinical and tumor-related outcomes in patients with nonfunctioning pituitary adenomas, while postoperative follow-up remained important.
Hefner & Cooper, 2025	Clinical review	Literature on recurrent/aggressive nonfunctioning PitNETs	Recurrent and aggressive tumors	Management of recurrent or aggressive tumors requires consideration of residual disease, anatomical extension, previous treatment, and the potential role of radiotherapy.
Castle-Kirszbaum *et al.*, 2024	Systematic review	Patients with nonfunctioning pituitary adenoma	Quality of life	Quality of life may remain impaired in patients with nonfunctioning pituitary adenomas despite treatment and requires consideration during long-term follow-up.
Bioletto *et al.*, 2024	Systematic review and meta-analysis	Patients with nonfunctioning pituitary adenoma	Mortality	Nonfunctioning pituitary adenomas are associated with excess mortality

	in pooled evidence, supporting the importance of long-term clinical surveillance.

The studies summarized in Table 1 represent different levels of evidence concerning the epidemiology, biological characteristics, clinical presentation, diagnostic evaluation, and treatment of PitNETs. Epidemiological and population-based studies establish the frequency and demographic characteristics of pituitary tumors, while recent pathological studies demonstrate the importance of transcription factor-based classification in defining tumor lineage (Daly & Beckers, 2020; Chen *et al.*, 2021). Molecular literature indicates that genetic, epigenetic, mitochondrial, and oxidative mechanisms interact in tumor development, with the relative contribution varying between tumor subtypes (Tatsi & Stratakis, 2019; Chang *et al.*, 2021). Clinical and treatment studies further demonstrate that management must account for hormonal activity, tumor extension, visual or neurological effects, residual disease, and recurrence rather than relying on tumor size alone (Fleseriu *et al.*, 2025; Hefner & Cooper, 2025). Overall, the available evidence supports an integrated interpretation of PitNETs based on epidemiological, molecular, pathological, endocrine, radiological, and clinical characteristics, while long-term outcomes remain influenced by tumor subtype, treatment response, recurrence, pituitary dysfunction, and quality of life (Bioletto *et al.*, 2024).

Discussion

The findings of this narrative review indicate that PitNETs represent a biologically and clinically heterogeneous group of anterior pituitary tumors whose presentation and management cannot be determined by tumor size alone. Epidemiological studies demonstrate that the reported incidence and prevalence of pituitary tumors vary between populations, partly because of differences in diagnostic practices and the increasing detection of previously unrecognized lesions through modern neuroimaging (Daly & Beckers, 2020). This increasing detection is particularly relevant for small and clinically silent tumors, which may remain asymptomatic until identified incidentally during imaging performed for other indications. At the same time, the clinical consequences of PitNETs range from isolated hormonal abnormalities to visual impairment, hypopituitarism, and locally invasive disease, emphasizing the importance of considering both endocrine activity and anatomical behavior when interpreting these tumors (Chen *et al.*, 2021). Therefore, the relatively indolent nature of most PitNETs should not be interpreted as an absence of clinically important morbidity (Casar-Borota *et al.*, 2024).

Evolution of Classification and Tumor Biology

One of the most important developments identified in the reviewed literature is the transition from the conventional term pituitary adenoma toward PitNET. The terminology introduced in recent WHO classifications reflects the neuroendocrine characteristics of these tumors and recognizes that their biological behavior ranges from indolent lesions to locally aggressive and, rarely, metastatic tumors (Asa *et al.*, 2022). This change is clinically

relevant because the traditional distinction between functioning and nonfunctioning adenomas describes hormonal activity but does not fully characterize tumor lineage or biological behavior. The 2022 WHO classification therefore places greater emphasis on pituitary transcription factors, particularly PIT1, TPIT, and SF1, together with hormone expression and cellular morphology, to establish lineage-based diagnoses (Asa *et al.*, 2022). Recent comparative data involving 921 cases further support the value of transcription factor-based classification and demonstrate that tumors classified under older systems may be reassigned when evaluated using the newer framework (Nasi Kordhishti *et al.*, 2025).

The introduction of lineage-based classification also has implications for the interpretation of clinically nonfunctioning tumors. Many tumors historically grouped as nonfunctioning or null cell adenomas can demonstrate a definable transcription factor lineage despite the absence of a clinically apparent hormone syndrome. Consequently, the absence of hormonal hypersecretion should not automatically be equated with the absence of biological differentiation. This distinction is particularly relevant for gonadotroph and other lineage-defined PitNETs, which may show hormone expression without producing a clinically recognizable endocrine syndrome. The current classification therefore provides a more biologically informative framework, although its ability to independently predict tumor behavior and guide treatment remains limited (Wan *et al.*, 2022). Recent literature emphasizes that no single pathological, radiological, or clinical characteristic is sufficient to predict aggressive behavior or malignant progression, supporting the need to integrate multiple clinical and biological variables (Casar-Borota *et al.*, 2024).

Molecular Pathogenesis

The reviewed evidence indicates that PitNET pathogenesis results from interactions among genetic alterations, intracellular signaling abnormalities, epigenetic mechanisms, and changes in cellular metabolism. Somatic mutations involving signaling pathways are particularly relevant to selected tumor subtypes, with *GNAS* alterations representing an established molecular abnormality in a proportion of somatotroph tumors (Tatsi & Stratakis, 2019). In contrast, germline abnormalities involving genes such as *MEN1* and *AIP* are more closely associated with familial or syndromic pituitary tumor predisposition and may be clinically relevant in patients with early-onset disease or a suggestive family history (Van den Broek *et al.*, 2019). These findings indicate that the molecular basis of PitNETs is heterogeneous and that the contribution of individual genetic abnormalities depends on tumor lineage and clinical context.

Epigenetic regulation provides an additional level of complexity in PitNET development. Altered DNA methylation, histone regulation, and microRNA expression have been associated with changes in gene transcription, cellular proliferation, hormone production, and tumor behavior (Chang *et al.*, 2021). Mitochondrial abnormalities may further influence cellular energy metabolism and oxidative stress, which are particularly relevant in endocrine cells characterized by active secretory processes (Wu *et al.*, 2024). Oxidative stress has also been proposed to influence the tumor microenvironment and signaling pathways involved in PitNET progression, although the extent to which these mechanisms can be translated into clinically useful biomarkers remains uncertain (Zhou *et al.*, 2023). Thus, molecular abnormalities currently provide important insight into tumor biology but have not yet replaced clinical, radiological, and pathological assessment in routine management.

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Clinical Manifestations and Their Relationship to Tumor Characteristics

The clinical spectrum of PitNETs reflects the interaction between hormone secretion and local tumor effects. Functioning tumors may produce recognizable endocrine syndromes, whereas clinically nonfunctioning tumors more often become symptomatic through mass effect or progressive impairment of normal pituitary function (Vieira *et al.*, 2016). This distinction is important because hormone-related symptoms may lead to earlier biochemical investigation, while nonfunctioning tumors may remain undetected until they become sufficiently large to affect the optic apparatus or normal pituitary tissue. Secondary hypothyroidism and other forms of hypopituitarism have been documented in patients with pituitary adenomas and are particularly relevant in larger lesions (Cahyanur *et al.*, 2018).

Tumor growth characteristics also appear to vary according to patient and tumor characteristics. Longitudinal evidence suggests that age and sex may be associated with different growth patterns among clinically nonfunctioning PitNETs, although these variables should not be considered independent predictors of individual tumor behavior (Park *et al.*, 2024). The clinical significance of tumor extension is especially important because invasion of the cavernous sinus or compression of the optic apparatus can influence both symptoms and the feasibility of complete surgical resection. Accordingly, anatomical evaluation should be integrated with endocrine findings rather than considered separately (Serioli *et al.*, 2019). This relationship explains why two tumors of similar dimensions may have substantially different clinical consequences depending on their location and biological characteristics.

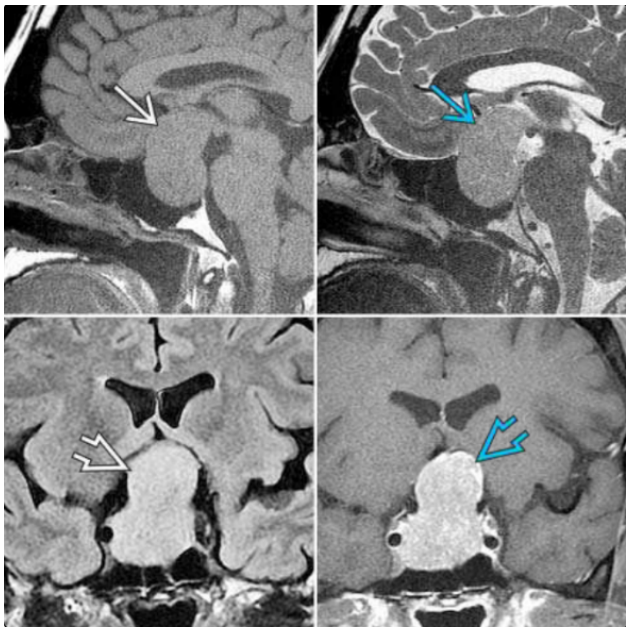

Figure 1. Sagittal MRI showing a sellar and suprasellar mass consistent with a macroadenoma
(Source: Osborn *et al.*, 2018).

Diagnostic Evaluation

The diagnosis of PitNETs requires integration of biochemical, radiological, ophthalmological, and pathological findings. Hormonal assessment should first determine whether a functioning tumor syndrome is present and should also evaluate the integrity of the remaining pituitary axes. This is particularly important because hormonal excess and

hormone deficiency may coexist in patients with larger or hormonally active tumors (Vieira *et al.*, 2016). When basal hormone concentrations are insufficient for diagnosis, appropriate dynamic testing may be required according to the suspected endocrine syndrome rather than applied uniformly to all patients (Lewis *et al.*, 2023). The interpretation of endocrine results should also account for physiological variation, medication effects, and assay-related limitations.

MRI remains the principal imaging modality for characterization of sellar and suprasellar lesions. Dedicated pituitary imaging provides information regarding tumor dimensions, suprasellar extension, optic chiasm involvement, cavernous sinus extension, and the relationship between the lesion and adjacent structures (Fleseriu *et al.*, 2025). Dynamic contrast-enhanced MRI may provide additional value in selected cases, particularly when a small functioning tumor is suspected but is difficult to identify on conventional sequences. However, imaging findings alone cannot establish the biological behavior of a PitNET. Radiological invasion may suggest more extensive disease, but it does not necessarily indicate aggressive or malignant behavior (Serioli *et al.*, 2019). The current diagnostic literature consequently favors an integrated interpretation of endocrine results, imaging characteristics, and pathological findings.

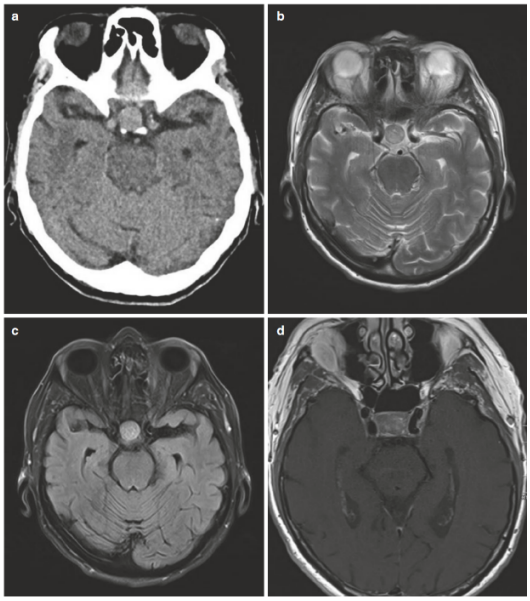

Figure 2. CT/MRI findings of a pituitary macroadenoma, including axial CT (a), coronal T2-weighted MRI (b), FLAIR (c), and contrast-enhanced axial T1-weighted MRI (d) (Source: Weis *et al.*, 2019)

Histopathology and Prognostic Interpretation

Histopathological examination has become increasingly important for defining the lineage of PitNETs rather than simply confirming the presence of a pituitary tumor. Immunohistochemical assessment of transcription factors such as PIT1, TPIT, and SF1 allows tumors to be assigned to specific developmental lineages and can clarify cases that would previously have been classified primarily according to hormone staining or as null cell tumors (Asa *et al.*, 2022). This approach is particularly valuable because hormone expression and clinical hormone secretion are not always equivalent. A tumor may express a particular hormone immunohistochemically without producing a clinically evident

endocrine syndrome, making transcription factor assessment an important component of modern pathological classification (Nasi Kordhishti *et al.*, 2025).

The interpretation of pathological features in relation to prognosis nevertheless requires caution. Ki-67 proliferation indices and other histological characteristics may provide information about proliferative activity, but no single marker is sufficient to classify a tumor as aggressive or predict malignant progression. Current evidence suggests that aggressive behavior is better understood through the interaction of clinical course, radiological characteristics, pathological findings, and, potentially, molecular alterations (Casar-Borota *et al.*, 2024). Therefore, pathological findings should contribute to risk assessment rather than serve as an isolated determinant of prognosis.

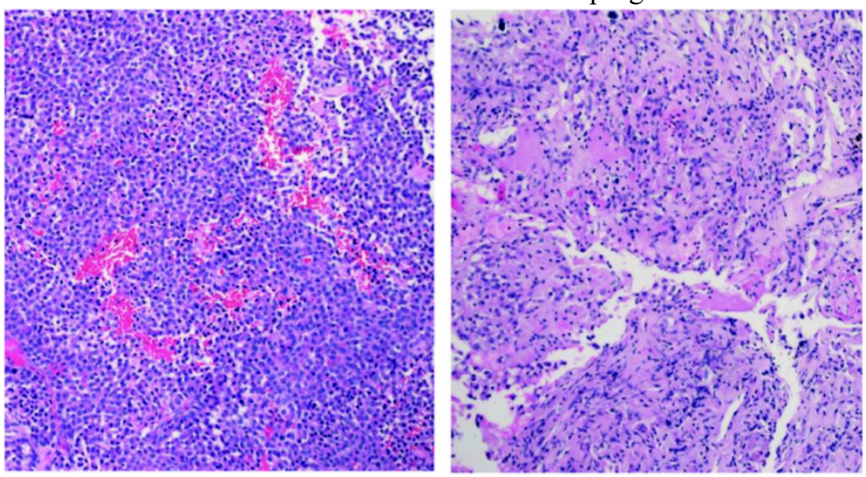

Figure 3. Microscopic comparison of corticotroph and somatotroph pituitary tumors (Source: Pecorari *et al*., 2022)

Management and Clinical Outcomes

The management of PitNETs is determined by tumor subtype, hormonal activity, anatomical extension, visual or neurological effects, and the presence of residual or recurrent disease. Medical therapy is particularly important for selected functioning tumors, while surgery is commonly considered when there is visual compromise, clinically significant mass effect, or another established surgical indication (Banskota & Adamson, 2021). For many sellar and suprasellar tumors requiring surgery, the transsphenoidal route provides access with less disruption of surrounding structures than transcranial procedures and has become the principal surgical route for appropriately selected lesions. Surgical outcomes, however, depend strongly on tumor size, invasion, relationship to the cavernous sinus and optic apparatus, and the ability to achieve adequate tumor removal without causing unacceptable pituitary or neurological injury (Choo *et al.*, 2022).

Transcranial surgery retains a role in selected giant or anatomically complex tumors when a transsphenoidal route cannot provide adequate access or decompression. Residual or recurrent disease may subsequently require additional surgery, radiotherapy, radiosurgery, or medical treatment depending on tumor subtype and location (Hefner & Cooper, 2025). The decision to use radiotherapy must consider the proximity of the lesion to the optic apparatus and other critical structures because treatment-related complications may emerge after a prolonged latency. Current management therefore favors individualized treatment planning rather than a single therapeutic strategy for all PitNETs (Fleseriu *et al.*, 2025).

Long-term clinical outcomes extend beyond radiological tumor control. Patients may continue to experience hypopituitarism, visual impairment, recurrence, treatment-related complications, or reduced quality of life even after apparently successful treatment (Castle-Kirszbaum *et al.*, 2024). In clinically nonfunctioning tumors, excess mortality has also been reported in pooled evidence, suggesting that apparently indolent tumor behavior does not eliminate the need for long-term endocrine and clinical surveillance (Bioletto *et al.*, 2024). These findings support follow-up strategies that assess endocrine function, visual status, tumor control, and patient-reported outcomes rather than relying solely on MRI measurements.

Implications for Clinical Practice

The synthesis of the available evidence suggests that the management of PitNETs is moving toward an integrated model that combines clinical endocrinology, neuroimaging, histopathology, and molecular characterization. The transition to transcription factor-based classification has improved the description of tumor lineage, but classification alone remains insufficient to predict the clinical course of individual tumors (Asa *et al.*, 2022). Similarly, advanced imaging and emerging molecular biomarkers may improve risk stratification, but their routine clinical utility remains under evaluation (Casar-Borota *et al.*, 2024). Recent literature therefore supports multidisciplinary evaluation, particularly for tumors with uncertain lineage, invasive growth, recurrent disease, or discordant clinical and pathological findings (Fleseriu *et al.*, 2025).

An important implication is that the term “nonfunctioning” should be interpreted as a clinical description rather than a complete biological classification. A patient may have no clinically apparent hormone hypersecretion while the tumor itself retains a definable pituitary lineage and may still cause substantial morbidity through mass effect or hypopituitarism. Conversely, a functioning tumor may be small but produce considerable systemic consequences because of hormone excess. The clinical importance of PitNETs therefore depends on the interaction between hormone secretion, tumor location, growth behavior, and effects on normal pituitary tissue rather than on tumor size or hormonal classification in isolation (Vieira *et al.*, 2016). This integrated interpretation is particularly relevant when determining surveillance intensity and treatment timing.

Limitations of the Current Evidence

The available literature also has several limitations that should be considered when interpreting the findings of this review. Epidemiological estimates vary because studies use different diagnostic criteria, populations, imaging practices, and definitions of clinically relevant tumors (Daly & Beckers, 2020). Molecular studies are similarly heterogeneous, and many reported molecular abnormalities are associated with particular tumor lineages rather than being universal mechanisms of PitNET development (Chang *et al.*, 2021). Evidence regarding aggressive behavior is particularly challenging because aggressive and metastatic PitNETs are uncommon, limiting the size and statistical power of available cohorts (Casar-Borota *et al.*, 2024).

Treatment studies also differ in surgical techniques, definitions of remission, follow-up duration, and criteria for recurrence. These differences make direct comparison between studies difficult and reinforce the importance of interpreting treatment outcomes within the context of tumor subtype and anatomical characteristics. Future studies involving larger multicenter cohorts and integrated clinical, pathological, and molecular

data may improve the ability to identify patients at increased risk of recurrence or aggressive progression (Casar-Borota *et al.*, 2024). Until such evidence becomes available, clinical decision-making should continue to rely on multidisciplinary assessment and individualized risk evaluation (Fleseriu *et al.*, 2025).

CONCLUSION

Pituitary neuroendocrine tumors (PitNETs) are heterogeneous anterior pituitary tumors with diverse hormonal, anatomical, pathological, and molecular characteristics. Their classification increasingly emphasizes transcription factor-based lineage determination, providing a more biologically relevant framework than hormone secretion alone. Clinical manifestations range from incidental lesions to endocrine syndromes, visual impairment, mass effect, and hypopituitarism; therefore, diagnosis requires integrated endocrine assessment, dedicated pituitary MRI, visual evaluation when indicated, and histopathological examination. Management should be individualized according to hormonal activity, tumor extension, visual or neurological involvement, and residual or recurrent disease, using medical therapy, transsphenoidal surgery, radiotherapy, or radiosurgery as appropriate. Long-term follow-up is essential because recurrence, persistent pituitary dysfunction, treatment-related complications, and impaired quality of life may occur, while further research is needed to clarify molecular markers and improve risk stratification for aggressive behavior.

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