REVIEW

The evolution in pituitary tumour classification: a clinical perspective

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Abstract

Objective: Pituitary tumours comprise a pathologically and clinically diverse group of neoplasms. Classification frameworks have changed dramatically in the past two decades, reflecting improving understanding of tumour biology. This narrative review examines the evolution of pituitary tumour classification, from a clinical perspective.
Results: In 2004, pituitary tumours were classified as 'typical' or 'atypical', based on the presence of markers of proliferation, Ki67, mitotic count and p53. In 2017, the new WHO marked a major paradigm shift, with a new focus on lineage-based classification, determined by transcription factor and hormonal immunohistochemistry. The terms 'typical' and 'atypical' were omitted, though the importance of proliferative markers Ki67 and mitotic count was acknowledged. The recent WHO 2022 classification incorporates further refinements, specifically recognising some less common types that may represent less well-differentiated tumours. Whilst 'high risk' tumour types have been identified, further work is still required to improve prognostication.
Conclusions: Recent WHO classifications have marked significant progress in the diagnostic evaluation of pituitary tumours, though shortcomings and challenges remain for both clinicians and pathologists in managing these tumours.

Introduction
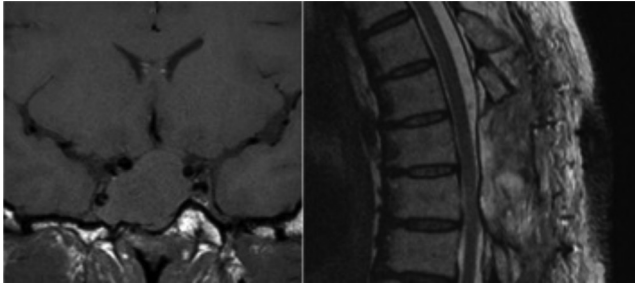
Pituitary tumours comprise a pathologically diverse group of neoplasms and exhibit a wide spectrum of clinical behaviour. Though occurring more commonly in radiology and autopsy studies, clinically apparent pituitary tumours have a prevalence of approximately 1 in 1000 people, presenting with hormonal hyper or hypofunction, and/or mass effect symptoms (Daly *et al.* 2006, Fernandez *et al.* 2010). In addition, 10–15% of tumours demonstrate 'aggressive behaviour', characterised by invasiveness with unusually rapid growth and/or

growth despite optimal therapies (McCormack *et al.* 2018, Raverot *et al.* 2018). More rarely, these may progress to develop distant metastatic disease (0.1–0.2%) (Fig. 1) (McCormack *et al.* 2018, Raverot *et al.* 2018). When surgery is undertaken in the management of pituitary tumours, the aims of pathological analysis are three-fold: (i) confirm the diagnosis of a pituitary tumour, distinguishing from other causes of sella-based lesions; (ii) classify the tumour type and (iii) provide prognostic information to assist clinicians in management plans. Over the last

Figure 1
Locally invasive pituitary tumour (left) and metastatic pituitary tumour (right).

few years, there have been significant developments in the pathological classification of pituitary tumours with a focus on cell lineage rather than hormonal expression. This followed the WHO 2017 classification recommending the incorporation of transcription factor immunohistochemistry (IHC) into the routine pathological analysis of pituitary tumours (Lloyd 2017). The recent WHO 2022 classification incorporates further refinement, specifically recognising some rarer types that may represent less well-differentiated tumours (Asa *et al.* 2022). Despite the acknowledgement of histological tumour types that may behave more aggressively, little progress has been made in improving prognostication. Measurement of Ki67 is still recommended; however, the tumour subclass of 'atypical adenoma', a new category in 2004, has been omitted in recent WHO classifications (DeLellis 2004, Lloyd 2017, Asa *et al.* 2022).

The diagnostic evaluation and prognostication of pituitary tumours continue to pose significant clinical challenges. Although there are well-recognised clinical and histopathological markers that can help predict adverse behaviour, some apparently unremarkable tumours progress to aggressive disease. In a recent cohort of 171 pituitary tumours, 14 progressed to clinically aggressive disease. Of these, 7 presented with a 'lower risk' histological type and Ki67 < 3%, features typically associated with benign behaviour (Lenders *et al.* 2021*b*) (Fig. 2). Conversely, some tumours with adverse features at presentation may not progress for many years. In such cases, the determinants of disease progression are not well understood and warrant further investigation.

This review presents a clinical perspective of the WHO classifications of adenohypophyseal pituitary tumours from 2004 to the recent 2022 edition, highlighting progress but also shortcomings and challenges that remain for both clinicians and pathologists in managing these neoplasms. It is beyond the scope of this review to discuss other unusual tumours of the pituitary, such as the pituitary blastoma or pituicytoma, or indeed other tumours of the sella region such as craniopharyngiomas or meningiomas. The authors have chosen not to discuss the proposed nomenclature change from 'pituitary adenoma' to 'PitNET', as described in the WHO 2022 classification, as this is the subject of significant ongoing debate, beyond the focus of this review. The term 'pituitary tumour' has therefore been adopted throughout this paper.

2004 WHO classification

The decade prior to the publication of the 2004 WHO classification had seen rapid evolution in pituitary tumour research, prompting numerous and varied attempts at classification systems, based on clinical manifestations, hormonal hypersecretion, size, histological characteristics, cellular composition, cytogenesis and growth pattern (Kovacs *et al.* 2001). The 2004 WHO defined three tumour types: typical, atypical and carcinoma (Table 1). 'Atypical adenomas' were defined by a Ki67 > 3%, excessive p53 immunoreactivity and increased mitotic activity, with these tumours thought to pose a higher risk of recurrence. 'Pituitary carcinoma' was used to describe those with cerebrospinal or distant metastases (DeLellis 2004). Importantly, there was a new emphasis on proliferative and other prognostic markers, reflecting a growing body of literature investigating factors that might help predict tumour outcomes (Al-Shraim & Asa 2006).

The 2004 WHO reflected tremendous progress in the understanding of pituitary tumours; however, it was broadly recognised to have several important shortcomings (Al-Shraim & Asa 2006). Although tumours were described with reference to cell lineages, these were not assigned as 'types' nor given separate ICD codes
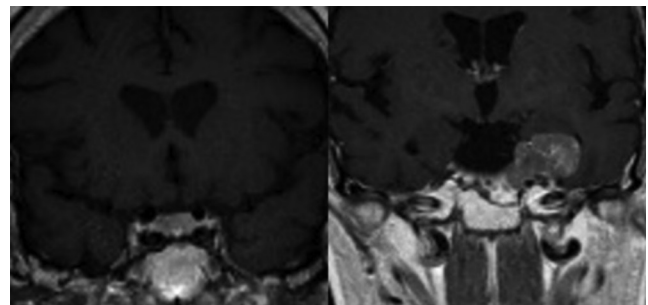
Figure 2
Corticotroph tumour (left) with subsequent progression to Nelson's Syndrome 5 years after initial resection (right).

Table 1 Evolution of WHO classification of pituitary tumours.

	2004 WHO	2017 WHO		2022 WHO	
Terminology	Adenoma	Adenoma vs tumour vs PitNET		PitNET	
IHC	Hormonal	TF & hormonal		TF & hormonal	
Type	'Typical'	*SF1 lineage*	Gonadotroph	*SF1 lineage*	Gonadotroph
	'Atypical'	*TPIT lineage*	Corticotroph	*TPIT lineage*	Corticotroph
		Pit1 lineage	Lactotroph (sparsely granulated, densely granulated, ASC)	*Pit1 lineage*	Lactotroph (sparsely granulated, densely granulated)
			Somatotroph (sparsely granulated, densely granulated, mammosomatotroph, mixed somatotroph- lactotroph)		Somatotroph (sparsely granulated, densely granulated)
					Mammosomatotroph[b]
					Mixed somatotroph and lactotroph[b]
			Thyrotroph		Thyrotroph
			Plurihormonal (PIT-1-positive plurihormonal[a], unusual combinations)		Mature plurihormonal PIT-1 lineage[c]
					Immature PIT-1 lineage[c]
					Acidophil stem cell[b]
		No distinct cell lineage	Null cell	*No distinct cell lineage*	Null cell
					Plurihormonal[c]
Proliferative markers	Ki67 > 3 %	Ki67 > 3 %			
	Elevated mitotic index	Elevated mitotic index			
	P53 ↑				
Carcinoma	Craniospinal or distant metastases	Craniospinal or distant metastases		Term omitted. Replaced with 'Metastatic PitNET'[c]	

[a]Newly defined in 2017 WHO classification; [b]Newly described as separate 'type' rather than 'subtype' in 2022 WHO classification; [c]Newly defined in 2022 WHO classification.
IHC, immunohistochemistry; TF, transcription factor.

(Al-Shraim & Asa 2006). Hence, the classification of tumours based solely on proliferative marker criteria did not attribute adequate prognostic importance to lineage, exemplified by our understanding of certain 'high risk' types, such as 'silent corticotroph' and 'silent subtype 3' tumours (Al-Shraim & Asa 2006). Moreover, we now know hormonal IHC to be less accurate than transcription factor analysis for lineage-based classification (Lenders *et al.* 2021*b*). Clinical application of the 2004 classification was limited, hampered by issues with the interpretation and reproducibility of proliferative markers. Of these, Ki67 is well recognised as the most reliable, though there remain issues with methodological standardisation and interobserver variability (Raverot *et al.* 2018). Proposed cut-offs heralding aggressive (3%) and metastatic (10%) disease are arbitrary and subject to considerable overlap in clinical practice, thus remaining somewhat controversial (Thapar *et al.* 1996, DeLellis 2004, Lloyd 2017). Nonetheless, elevation in Ki67 has been associated with tumour recurrence and metastatic disease, with higher levels reported in distant deposits compared with their

primary counterparts (Thapar *et al.* 1996, Saeger *et al.* 2007, 2008, Kovacs *et al.* 2015, Lenders & McCormack 2018). Similarly, increased mitotic count has been associated with an increased risk of recurrence and metastatic disease (Miermeister *et al.* 2015, Lenders & McCormack 2018, Raverot *et al.* 2018). The 2004 WHO did not assign a clear cut-off for P53 immunopositivity, with resultant subjective and varied interpretation from different laboratories around the world, limiting reproducibility for research and clinical purposes (Al-Shraim & Asa 2006, Trouillas *et al.* 2013).

2017 WHO classification

The 2017 WHO classification marked a major paradigm shift in pathological evaluation of pituitary tumours. Typing of tumours was now based on cell lineage, determined by immunohistochemical expression of transcription factors and anterior pituitary hormones (Table 1) (Lloyd 2017). The term 'atypical' was omitted;

Ki67 and mitotic count were acknowledged as important prognostic markers, whilst p53 was excluded (Mete & Lopes 2017, Inoshita & Nishioka 2018, Lopes 2020). Importantly, lineage-based classification allowed for the identification of 'high risk' histological subtypes, which were suggested to be associated with recurrent and/or aggressive behaviour (Nishioka *et al.* 2015, Lenders *et al.* 2021*b*).

Transcription factors determine cellular commitment and differentiation, driving the maturation of cells from the Rathke's pouch to acidophil, gonadotroph and corticotroph lineage. Pituitary-specific POU-class homeodomain transcription factor (PIT-1) gives rise to acidophil cell lineage. Somatotroph cells are formed under the direction of PIT-1. Estrogen receptor-alpha (ER-α) is a nuclear receptor activated by oestrogen, which in turn activates the prolactin promoter, in conjunction with PIT-1, giving rise to mammosomatotroph cells (Lv *et al.* 2012). This process leads to mature lactotroph cells, following downregulation of growth hormone (GH) expression, though the mechanism is unknown. Similarly, thyrotroph cell differentiation requires PIT-1 and GATA2/3 expression, in combination with suppression of GH. Transdifferentiation occurs between PIT-1 lineage types throughout the normal life cycle, as determined by developmental requirements. Steroidogenic factor 1 (SF-1) gives rise to gonadotroph cell differentiation and T-box family member TBX19 (T-PIT) drives differentiation of the corticotroph lineage (Lopes 2017, Asa 2021) (Fig. 3).

Refinement of classification

The application of transcription factor IHC has been associated with refinement in the lineage-based classification of tumours, particularly those with weak or absent hormonal IHC. Null cell tumours have traditionally been defined as clinically silent tumours with absent hormonal immunoexpression; previously thought to account for 20–30% of non-functioning pituitary tumours (NFPT) (Nishioka *et al.* 2015, Almeida *et al.* 2019). Clinically silent tumours are those not associated with clinical or biochemical features of hormone hypersecretion (Drummond *et al.* 2019). In the 2017 WHO, null cell tumours were classified as tumours arising from adenohypophyseal cells without evidence of cell lineage differentiation, specifically characterised by the absence of hormonal and transcription factor immunoexpression (Lloyd 2017). To date, two studies have reported on the outcomes of the application of transcription factor IHC to evaluate cellular lineage. Nishioka and colleagues applied transcription factor IHC to a cohort of 516 NFPT. Application of transcription factor IHC permitted reclassification of 95% (113/119) of hormone immunonegative tumours, yielding only six true null cell tumours (Nishioka *et al.* 2015). More recently, we have applied transcription factor IHC to 171 pituitary tumours of all hormonal types (Lenders *et al.* 2021*b*). In this cohort, there were 20 tumours that were reclassified following transcription factor analysis, including all five hormone
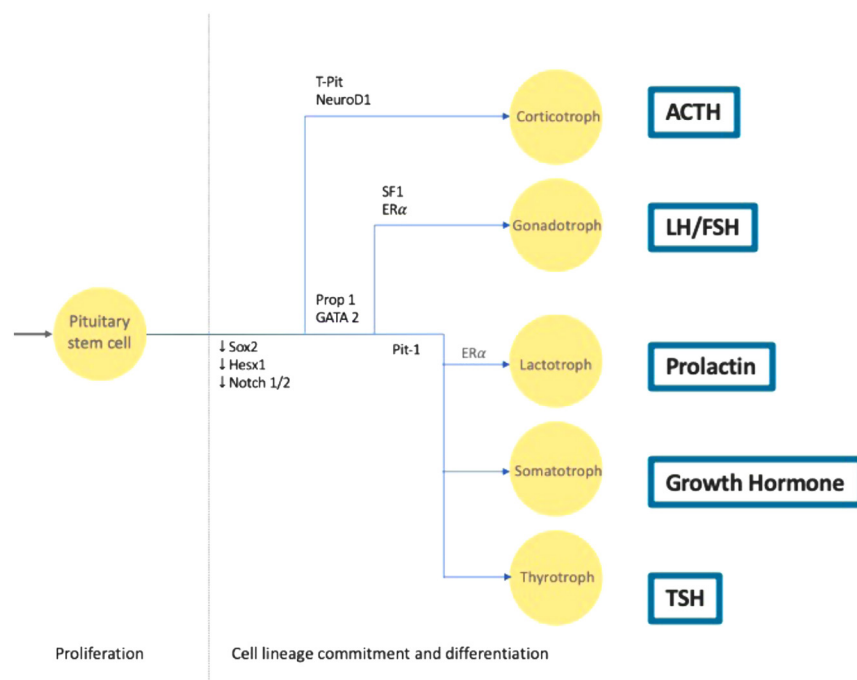
Figure 3
Transcription factors involved in cell lineage commitment and differentiation (from Lenders *et al.* (2021*a*).

immunonegative tumours. Whilst both studies reported a marked reduction in the number of null cell tumours once transcription factor analysis was applied, there is a disparity between the results, which may be accounted for by key methodological differences between studies. The former reported on NFPT only, whereas the latter reported on tumours of all types. Perhaps more importantly, this discrepancy highlights the lack of consensus regarding the diagnostic thresholds for the interpretation of IHC (Nishioka *et al.* 2015, Lenders *et al.* 2021*b*).

Newly defined: PIT-1 plurihormonal tumours

The 2017 WHO Classification also redefined PIT-1-positive plurihormonal, or 'poorly-differentiated PIT-1 plurihormonal' tumours, previously known as 'silent subtype 3'. Pathologically, these were defined by PIT-1 immunopositivity and nuclear atypia, with or without presence of lineage-specific hormone immunoexpression (Mete *et al.* 2016, Mete & Lopes 2017). Despite the recent nomenclature change, further revisions were soon being called for in the literature (Asa 2021). Authors argued that the term 'poorly-differentiated' holds an association with high-grade neuroendocrine malignancies, causing confusion about the nature of PIT-1-positive plurihormonal tumours (Asa 2021).

Prognostic implications of lineage-based classification

Advent of lineage-based classification with the 2017 WHO led to a paradigm shift in tumour prognostication. 'High risk' histological subtypes were identified and proposed to be associated with recurrence and/or aggressive behaviour: silent corticotroph, PIT-1-positive plurihormonal, sparsely granulated somatotroph, lactotroph in men and Crooke's cell tumours. Additionally, tumours such as acidophil stem cell adenoma, densely granulated lactotroph and thyrotroph, though not listed as 'high risk' per se, were noted in the text to have a higher risk of aggressive behaviour (Lloyd 2017). However, evidence supporting this stratification was limited, hampered by the rarity of some of these tumour types and varied classification criteria. Recently, 'high-risk' histological types have been associated with tumour invasiveness, earlier recurrence and lower recurrence-free survival (Lenders *et al.* 2021*b*). This study grouped the 'high risk' types together, a limitation that fails to account for the broad heterogeneity of these tumours.

Silent corticotroph tumours

Silent corticotroph tumours (SCT) are defined by the absence of clinically or biochemically apparent hormone hypersecretion, with immunopositivity for adrenocorticotrophic hormone (ACTH) and/or T-PIT. A few small studies have examined the prevalence and prognosis of these tumours, with mixed results. Importantly, evidence suggests that the prevalence of silent corticotroph tumours has been substantially underestimated in hormonal IHC alone. In our cohort, we found an increase from 9 to 16 SCT in a cohort of 171 following the addition of transcription factor analysis, compared to hormonal IHC alone (Lenders *et al.* 2021*b*). Of these cases, one had been previously diagnosed as a silent prolactin tumour with low proliferative markers (Ki67 and mitotic count) and progressed to aggressive disease (Lenders *et al.* 2021*b*). Similarly, Zhang and colleagues reported 105 SCT in a cohort of 757 operatively managed NFPT, of which 66 were ACTH immunonegative (Zhang *et al.* 2020). The data regarding prognostic outcomes of these tumours are limited, with most studies predating the 2017 WHO classification. A 2018 meta-analysis compared the recurrence/ regrowth of SCT with other clinically non-functioning types (Fountas *et al.* 2019). Recurrence was defined as radiological progress or regrowth of tumour. Based on 14 included studies (197 patients), the SCT recurrence rate was 5.96 per 100 person-years. There were 10 eligible studies for comparison of silent corticotroph ($n = 244$) and other non-functioning tumours ($n = 1622$), with recurrence in 31% of SCT and no significant difference in the risk of recurrence between groups. Importantly, the meta-analysis also compared groups treated with surgery and radiotherapy vs surgery alone, with consistent findings. The shortcomings of included studies must be noted: all predated 2017 WHO classification; comparator non-functioning groups were of mixed subtypes; follow-up periods were relatively short (2–7.4 years) and varied across groups as well as studies (Fountas *et al.* 2019, Lenders *et al.* 2021*b*).

At the time of writing, only one study has examined the clinical characteristics of corticotroph tumours following the adoption of lineage-based diagnosis. Jiang and colleagues compared outcomes for 112 silent corticotroph and 198 gonadotroph tumours, following primary or recurrent surgery, with follow-up to 22 months (Jiang *et al.* 2021). In this study, the application of transcription factor IHC increased the detected prevalence of SCT from 21.3 to 30.2%. These had a female preponderance, were more invasive and demonstrated

more cystic change than their gonadotroph counterparts. Rates of gross total resection, recurrence and progression did not vary significantly between groups. Strengths of this study include large numbers and the application of lineage-based classification. Important weaknesses include relatively short follow-up and inclusion of both primary and subsequent operations, both of which have significant implications for positive and negative study findings (Jiang *et al.* 2021). Although data regarding the overall outcomes of SCT are inconclusive, studies have consistently reported that there is a subset of these tumours that behave aggressively (Fountas *et al.* 2019, Drummond *et al.* 2019).

Sparsely granulated somatotroph tumours

Somatotroph tumours account for approximately 10–15% of all resected pituitary tumours and can be sub-classified according to their cytokeratin staining pattern (Mete & Lopes 2017). Densely granulated tumour cells are characterised by peri-nuclear cytokeratin staining. Sparsely granulated tumour cells have characteristic juxtanuclear fibrous bodies, in over 70% of cells, with a histological dot-like appearance (Mete & Lopes 2017). Sparsely granulated somatotroph tumours have been associated with larger size, invasiveness, aryl hydrocarbon receptor-interacting protein (AIP) mutations, lower SSTR2 expression and poor response to somatostatin receptor ligands (Brzana *et al.* 2013, Heng *et al.* 2021, Swanson *et al.* 2021). Clinically silent somatotroph tumours are more frequently sparsely granulated (Chinezu *et al.* 2017). Radiologic and radiomic studies have demonstrated a correlation between imaging characteristics and granulation, expanding the potential for pre-operative prediction of tumour behaviour (Park *et al.* 2020, Swanson *et al.* 2021).

PIT-1 plurihormonal tumours

'PIT-1-positive plurihormonal tumours', under the framework of differing nomenclature, have been associated with a propensity for progressive disease (Horvath *et al.* 2005, Erickson *et al.* 2009, Mete *et al.* 2016). In a retrospective review of 27 'silent subtype 3 adenomas', Erickson and colleagues highlighted the heterogeneous nature of the clinical and pathological presentation of these rare tumours, with endocrine hyperfunction in just 30% of cases, invasiveness in 60% and recurrence after complete resection in 37% (Erickson *et al.* 2009). In a cohort of 31 patients, Mete *et al.* similarly reported heterogeneity in immunohistochemical findings, ranging

from absence to diffuse positivity for multiple hormones (Mete *et al.* 2016). Residual tumour was present in 65% of cases, with disease progression in 53% over a mean follow-up period of 48.4 months. Improved diagnostic techniques and classification continue to approximate our evolving understanding of these tumours.

Lactotroph tumours in men

Lactotroph tumours comprise between 25 and 57% of all pituitary tumours (Gillam *et al.* 2006, Gruppetta *et al.* 2013). The spectrum of disease is broad, ranging from benign through to metastatic disease (Trouillas *et al.* 2019). There is a clear female preponderance reported (10:1); at least partly attributable to inherently more clinically apparent disease in women of reproductive age (Colao *et al.* 2003, Ciccarelli *et al.* 2005). Indeed, differences in lactotroph tumour prevalence by gender are not observed in patients aged over 50 years (Colao *et al.* 2003, Kars *et al.* 2009). Male patients are more likely to present with larger, more invasive tumours that are resistant to dopamine agonists and require multimodal therapy (Delgrange *et al.* 1997, Delgrange *et al.* 2015, Liu *et al.* 2018, Trouillas *et al.* 2019). In a retrospective surgical cohort study of 94 patients with lactotroph tumours, Raverot *et al.* reported an association between male gender and post-operative persistence but not recurrence, albeit on univariate analysis only (Raverot *et al.* 2010). These findings are corroborated in paediatric groups and in patients correlated for age at diagnosis (Delgrange *et al.* 1997, Salenave *et al.* 2015). Tumour expression of ER-α is less in male compared with female patients, thought to reflect poorer differentiation, which in turn has been correlated with aggressiveness and worse prognosis (Delgrange *et al.* 2015, Trouillas *et al.* 2019). There is clear evidence demonstrating aggressive behaviour in male lactotroph tumours, though the pathophysiology and predictors of clinical course remain poorly understood.

Acidophil stem cell tumours

Acidophil stem cell tumours are rare, with an overall prevalence of approximately 0.2%. Studies investigating acidophil stem cell tumour biology and prognostication have been limited to a few case series and case reports (Horvath *et al.* 1981, Page *et al.* 1996, Maheshwari *et al.* 2000, Saeger *et al.* 2007, Annapurni & Rathi 2019). These tumours are thought to derive from the acidophil cell line and have been described as 'immature' neoplasms (Asa 2021). Clinical presentation is common with

hyperprolactinaemia, whilst few patients exhibit features of acromegaly (Horvath *et al.* 1981, Annapurni & Rathi 2019). Interestingly, clinical acromegaly has been reported without congruent biochemical findings, raising suspicion of biologically active GH hypersecretion not detected by current assays (Horvath *et al.* 1981, Annapurni & Rathi 2019). The natural history is characteristically rapid (months to 5 years), with local invasion, relatively low hormonal hypersecretion and resistance to dopamine agonist therapy (Horvath *et al.* 1981, Huang *et al.* 2006, Annapurni & Rathi 2019). In a case series of 15 patients with acidophil stem cell tumours, Horvath *et al.* described immature neoplasms characterised by a single cell type, assumed to be the common committed progenitor of GH and prolactin producing cells (Horvath *et al.* 1981). Most tumours were found to have prolactin-producing cells, with few producing GHs. The authors highlighted the importance of electron microscopy, required to identify the presence of incompletely differentiated cellular components (including giant mitochondria and sparse hyaline bodies), distinguishing these from mixed GH/PRL and somatomammotroph tumours (Horvath *et al.* 1981). Importantly, this study predated the adoption of transcription factor analysis.

Crooke's cell tumours

'Crooke's hyaline change' describes the presence in the cytoplasm of a dense ring-like band of cytokeratin positive, intermediate filaments that form as a response to glucocorticoid feedback in T-PIT lineage cells. Occasionally, this change gives rise to Crooke's cell tumours, which are hormonally suppressed T-PIT tumours, with characteristic cytoplasmic ring-like hyaline change (Asa 2021). Although little is known about the pathogenesis of these tumours, several studies have reported on their invasiveness, recurrence and progression to carcinoma (Heaney 2011, 2014). One case series described 31 patients with Crooke's cell tumours, of which 60% demonstrated recurrence and 2 progressed to metastatic disease (George *et al.* 2003).

2022 WHO classification

In 2022, a new WHO classification was released (Asa *et al.* 2022, WHO 2022). There is significant debate concerning the proposed nomenclature change from 'pituitary adenoma' to 'pituitary neuroendocrine tumour' (PitNET) in this edition, which is covered in detail elsewhere (Ho

et al. 2019, Asa *et al.* 2020). Transcription factor-based diagnostic criteria were broadly upheld, with further refinements to classification, summarised later and in Tables 1 and 2. Additionally, a new type of pituitary tumour was described within the 'tumours with no distinct cell lineage' category, 'plurihormonal tumour' (WHO 2022).

Refinement of classification: immature PIT-1 lineage tumours and mature PIT-1 plurihormonal tumours

The 2022 WHO newly defined two separate tumour types: 'Immature PIT-1 lineage' and 'mature plurihormonal PIT-1 lineage' tumours, addressing the heterogeneity within the group previously known as 'Silent subtype 3' or 'Pit-1-positive plurihormonal' tumours from 2017 (WHO 2022). 'Immature PIT-1 lineage tumours' are characterised by polygonal or chromophobic cells, PIT-1 immunopositivity, variable hormonal immunoexpression and cells that lack features of terminal differentiation. Clinically, these may present with or without hormonal hypersecretion, tend to be associated with large unresectable tumours, aggressive behaviour and have been linked with MEN1 (Asa *et al.* 2022). Conversely, the other newly defined 'mature plurihormonal PIT-1 lineage tumours' are characterised by monomorphic mature tumour cells, with PIT-1 immunopositivity and variable PIT-1 lineage hormone expression (Asa *et al.* 2022). In practice, the apparent overlap of the stated criteria for these tumours makes definitive classification problematic. The new WHO classification has come a long way in reflecting the great heterogeneity in these tumour types; however, understanding of the biology of the 'immature' type remains somewhat limited (Horvath *et al.* 2005, Erickson *et al.* 2009, Mete *et al.* 2016, Lenders *et al.* 2021*b*).

Newly defined: tumours with no distinct cell lineage

The application of transcription factor IHC has given rise to the identification of a group of tumours not meeting the criteria for any defined tumour type (Lloyd 2017, Asa *et al.* 2022). In the 2022 WHO, these were acknowledged within a separate category, 'tumours with no distinct cell lineage', with a newly defined type 'plurihormonal tumours' along with previously defined 'null cell tumours' (Table 1). The newly defined 'plurihormonal tumour' type was described as 'very rare', comprising a monomorphous population of cells that display features of multiple lineages (Asa *et al.* 2022). These have been the subject of case reports only, and their biology is not yet fully understood (Tahara *et al.* 2002, Mete *et al.* 2018,

Table 2 The 2022 WHO classification of pituitary tumours.

Type	Subtype	Transcription factors	Hormones
PIT-1 lineage			
Somatotroph tumours	Densely granulated somatotroph tumour	PIT-1	GH, ∝-subunit
	Sparsely granulated somatotroph tumour	PIT-1	GH
Lactotroph tumours	Sparsely granulated lactotroph tumour	PIT-1, ER∝	PRL (paranuclear dot-like)
	Densely granulated lactotroph tumour	PIT-1, ER∝	PRL (diffuse, cytoplasmic)
Mammosomatotroph tumour		PIT-1, ER∝	GH (predominant), PRL, ∝-subunit
Thyrotroph tumour		PIT-1, GATA3	∝-subunit, βTSH
Mature plurihormonal PIT-1 lineage tumour		PIT-1, ER∝, GATA3	Monomorphic tumour cells with predominant GH expression, variable other PIT-1 lineage hormones
Immature PIT-1 lineage tumour		PIT-1 (ER∝, GATA3)	Monomorphic tumour cells with focal/variable staining for no hormones, or one or more of the PIT-1 lineage hormones
Acidophil stem cell tumour		PIT-1, ER∝	Monomorphic tumour cells with PRL (predominant) and GH (focal, variable)
Mixed somatotroph and lactotroph tumour		PIT-1, ER∝	Two morphologically distinct cell populations: GH, PRL
T-PIT lineage			
Corticotroph tumours	Densely granulated corticotroph tumour	T-PIT	ACTH and other POMC derivatives
	Sparsely granulated corticotroph tumour	T-PIT	ACTH and other POMC derivatives
SF-1 lineage			
Gonadotroph tumour		SF-1, ER∝, GATA3	∝-subunit, LH, FSH, or none
Tumours with no distinct cell lineage			
Plurihormonal tumour		Multiple combinations	Multiple combinations in a monomorphous population
Null cell tumour		None	None

Tordjman *et al.* 2019). One study hypothesised that they may arise from immature cells, though this has not been proven (Tordjman *et al.* 2019). Importantly, transcription factor analysis remains limited to research and tertiary centres; therefore, the true prevalence of these tumours remains to be determined.

Tumour prognostication

The 2022 WHO highlighted several key changes in the approach to pituitary tumour prognostication (Asa *et al.* 2022, WHO 2022). Notably, the post-operative predictive value of Ki67, mitotic count and p53 were brought into question. Proliferative marker diagnostic cut-offs were not delineated as they had been in previous editions. Instead, the prognostic focus was shifted towards 'high risk' tumour types: immature PIT-1 lineage, silent corticotroph, null cell, sparsely granulated somatotroph and acidophil stem cell tumours (Lenders *et al.* 2021a, WHO 2022). Within individual lineages, the new classification identified

possible predictive markers, such as SSTR expression in somatotroph tumours, marking a shift towards type-specific prognostication (Antunes *et al.* 2018, Asa *et al.* 2022). The prognostic importance of tumour invasiveness, gross total resection and post-operative growth rate were also emphasised.

Ongoing challenges in real-world application of 2017 and 2022 WHO classifications

Refinements in lineage-based classification in 2017 and 2022 have been important in propelling understanding of pituitary tumour biology and show promise for improving prognostication. However, widespread clinical application of the current WHO classification requires clarification of diagnostic cut-offs, streamlining of laboratory techniques and stratification of immunohistochemical processes to allow for economic feasibility. Moreover, prognostication remains challenging in clinical practice.

Diagnostic reproducibility and interpretation

Both the 2017 and 2022 WHO classifications failed to define a clear cut-off for transcription factor immunopositivity, posing a shortcoming in diagnostic reproducibility (Lloyd 2017, WHO 2022). Studies to date have implemented differing diagnostic criteria, compounding the issue. Nishioka *et al.* reported transcription factor positivity in tumours expressing immunoreactivity in at least 80% of tumour cells (Nishioka & Inoshita 2018). By comparison, Torregrosa-Quesada *et al.* considered tumours with 5% positive cells to be immunopositive (Torregrosa-Quesada *et al.* 2019). Finally, we have considered tumours with 10% positive tumour cells to be immunopositive, though those with 10–30% positive cells were deemed to form a grey area and are individually reviewed (Lenders *et al.* 2021*b*). Whilst 80% immunopositivity may give rise to overdiagnosis of null cell tumours, 5% immunopositivity might, in turn, be associated with either overdiagnosis of a plurihormonal tumour or misinterpretation of residual normal anterior pituitary parenchymal cells. We propose that 10% immunopositivity offers a clinically meaningful cut-off for real-world applications, where no other transcription factors are expressed (Lenders *et al.* 2021*b*). Putting such thresholds aside, in our pathological practice, PIT-1 is almost always expressed across all tumour cells (>90% of cells) in PIT-1-positive tumours, T-PIT-positive tumours typically show a mosaic pattern with positivity in around 70% of the tumour cells. Amongst gonadotroph tumours, SF-1 may vary from patchy (around 20% expression) through to widespread (>90%) expression in tumour cells. The accuracy and reproducibility of immunohistochemical assessment may be improved by automated image analysis algorithms in the future, though data in this area are currently lacking (Asa *et al.* 2022). In any case, laboratory interpretation may have profound effects on the precision of diagnosis and hence prognostic capacity of classification, with impacts in research and clinical practice.

Antibody preparation and availability

Clinical experience and application of lineage-based classification remain very limited (Nishioka *et al.* 2015, Lenders *et al.* 2021*b*). Adoption of transcription factor analysis by clinical laboratories has been slow, hampered by experiential and financial constraints. Compounding the issue, there are no guidelines regarding the selection, preparation or interpretation of commercially available antibodies for recommended transcription factors. Nishioka *et al.* reported the selection of antibodies against adenohypophyseal cell lineage transcription factors but did not provide protocols for the preparation of antibodies, some of which were not commercially available (Nishioka *et al.* 2015). We have previously described details of commercially available antibodies and their optimisation protocols. However, we found challenges in acquiring and implementing the SF-1 antibody, an issue which may also be encountered in other clinical laboratories (Lenders *et al.* 2021*b*). Similarly, Torregrosa-Quesada *et al.* reported on commercially available antibodies, although did not provide optimisation protocols (Torregrosa-Quesada *et al.* 2019). Selection and application of antibodies have major implications for the determination of cell immunopositivity, and hence diagnostic accuracy.

Economic feasibility

The recent 2022 WHO classification has recognised that economic feasibility is a pivotal determinant of widespread clinical uptake of transcription factor analysis, both in wealthy and lesser developed countries. Expansion of diagnostic IHC comes at increased cost and burden of laboratory work. Although there are no published data regarding the cost of transcription factor IHC, the authors can provide estimates based on experience within a tertiary referral centre (St Vincent's Hospital, Sydney, Australia): $50 AUD per immunostain per patient, equating to an increase in cost from $300 AUD to $450 AUD per pituitary tumour evaluation, which includes the relevant pituitary hormones plus SF-1, T-PIT and PIT-1 transcription factors (Lenders *et al.* 2021*b*).

Several studies have proposed stratified algorithms for the evaluation of pituitary tumours. The European Pituitary Pathology Group suggested a tiered approach to diagnosis in 2017, commencing with evaluation of functional status, followed by hormonal IHC and cytokeratin staining, then transcription factor analysis in certain situations only (Villa *et al.* 2019). Importantly, rarer tumour lineage types may be missed by this approach. Another algorithm was proposed by McDonald *et al.* in 2017, then revised in 2021 with the addition of T-PIT, previously omitted due to lack of commercial availability. This comprised a one- or two-step algorithm: (i) transcription factor IHC and (ii) IHC for prolactin, GH, thyroid-stimulating hormone and cytokeratin CAM5.2 for cases that were not clearly gonadotrophic, corticotrophic or null cell (McDonald *et al.* 2017, 2021). Although the algorithm was able to reduce the required IHC stains by approximately 30%, rarer lineage types may again be missed. A more recent publication proposed a tiered approach for the application of the 2022

WHO, with 100% concordance and 34% cost reduction, compared with clinical evaluation and a complete panel of transcription factor and hormone IHC (Lenders *et al.* 2022). The aforementioned algorithms demonstrate that workflow efficacy may be greatly improved whilst maintaining considerable diagnostic accuracy.

Tumour prognostication

Prognostication of pituitary tumours remains challenging (McCormack *et al.* 2018, Raverot *et al.* 2018, Asa *et al.* 2022). Various clinical, radiological and pathological factors are well known to predict behaviour over time: patient age, tumour size, location, invasiveness and markers of proliferation (McCormack *et al.* 2018, Raverot *et al.* 2018). Yet, post-operative practices remain largely centre dependent and are guided by physician and/or multi-disciplinary team decisions. The evolving WHO classification continues to fall short of tying together the various factors known to be important in the evaluation of pituitary tumours, although the most recent edition does call for a multidisciplinary consensus predictive score (DeLellis 2004, Trouillas *et al.* 2013, Lloyd 2017, Asa *et al.* 2022, WHO 2022). The 2022 WHO places emphasis on determining pituitary tumour types, some of which are known to be 'high risk', and identifies biomarkers relevant to particular lineages (Asa *et al.* 2022). There are numerous such biomarkers that have been proposed in the literature but are yet to be incorporated into clinical practice (Lenders *et al.* 2021*a*).

The use of proliferative markers such as mitotic count and Ki67 has been largely sidelined in the 2022 WHO classification. Methodology for assessment of proliferative markers and cut-offs for positivity has not been included, despite such details being included in the same edition pertaining to neuroendocrine tumours of the digestive tract (WHO 2022). We anticipate future consensus on the methodology used for the assessment of Ki67 and mitoses in pituitary tumours and a clear cut-off to denote their elevation would be particularly useful for clinicians and pathologists in both the clinical and research setting. Until such time following the methodology described for neuroendocrine tumours of the digestive tract seems the most appropriate for use (WHO 2022).

In 2013, Trouillas *et al.* proposed a five-tiered clinicopathological classification, determined by tumour invasiveness and proliferative activity (at least two of three pathological markers, Ki67 ≥ 3%, mitotic count ≥ 2 per 10 high-powered field and elevated p53) (Trouillas *et al.* 2013) (Table 3). In a retrospective cohort study, invasive and

Table 3 Trouillas clinicopathological classification of tumours.

Imaging characteristics	Histopathology	Grade
Non-invasive	Non-proliferative	1a
	Proliferative[a]	1b
Invasive[b]	Non-proliferative	2a
	Proliferative[a]	2b
	Metastatic	3

[a]At least two of three pathological markers, Ki67 ≥ 3%, mitotic count ≥ 2 per 10 high powered field and elevated p53; [b]On histopathology or radiology.

proliferative tumours (grade 2b) had a 12-fold increased risk of recurrence when compared with non-invasive and non-proliferative counterparts (grade 1a), over 8 years of follow-up (Trouillas *et al.* 2013). In a subsequent prospective cohort study of 365 patients, grade 2b tumours had a 3.72-fold risk of recurrence, compared with grade 1a, over a median of 3 years (Raverot *et al.* 2017). In a more recent retrospective cohort of 120 clinically NFPT, grade 2b tumours had a 66% probability of recurrence at 5 years compared with 20% in the grade 1a tumours (Lelotte *et al.* 2018). Although this method of tumour grading marked a significant advance in prognostication, it fails to account for the considerable variability in the clinical course of different lineage types, highlighted in recent studies and the 2022 WHO (Lenders *et al.* 2021*b*, WHO 2022). Moreover, it utilises p53 protein expression, which is now recognised to have poor reproducibility, an uncertain biological basis and limited clinical significance. From a different vantage point, results from the ESE Survey in 2018 defined clinically 'aggressive' tumours as those with 'radiologically invasive tumour and unusually rapid growth or clinically relevant tumour growth despite optimal standard therapies' but failed to link clinical parameters to important pathological markers (McCormack *et al.* 2018, Raverot *et al.* 2018, Lenders *et al.* 2021*b*).

Conclusions and areas for future research

Lineage-based classification has led to an important paradigm shift in the diagnostic approach to pituitary tumours. In 2017, WHO classification proposed the application of transcription factor and hormonal IHC for lineage-based classification of tumours. The 2022 WHO validated the role of lineage-based classification with further refinements to classification and emphasis on utility in prognostication. Unlike prior editions, the 2022 WHO made little acknowledgement of a prognostic role for

proliferative markers, Ki67 and mitotic count (Lloyd 2017, Asa *et al.* 2022, WHO 2022). The evolving classification marks a shift towards lineage-based prognostication, with specific biomarkers to be delineated for each tumour type.

There is still no consensus regarding the cut-off required to define positivity on IHC, for transcription and other markers such as Ki67. The new classification system also poses new challenges and areas for improvement. Additional cost and workload could be limited by a tiered approach to pathological evaluation (Lenders *et al.* 2022). Standardisation of laboratory practices and diagnostic cut-offs will be vital for reproducibility, both in research and clinical settings. Finally, refinements in classification have highlighted areas of tumour biology that remain poorly understood. Future studies should aim to continue to improve understanding of biology and prognostication of pituitary tumours. This will be important for identifying new targets for directed therapies and refining care for patients, based on a better understanding of tumour outcomes. Multi-centre international prospective studies are required to elucidate interactions of new and known predictive markers, ultimately enabling earlier and targeted therapies.

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