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# Selected updates in thyroid, parathyroid, and adrenal gland pathology

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ABSTRACT

Endocrine pathology is continuously advancing with with new classification systems and an increased understanding the underlying pathogenesis and genetic alterations, whether somatic or germline, in endocrine diseases. Many changes have recently occurred in the classification of thyroid carcinoma, the most complex of which involve the new category of "high-grade follicular cell derived non anaplastic thyroid carcinoma" which encompasses both poorly differentiated thyroid carcinomas and differentiated high-grade thyroid carcinomas. The word "hyperplasia" is no longer used with primary multiglandular parathyroid disease due to increased understanding of its clonal nature. New terminology of "atypical parathyroid tumor" has been introduced for tumors highly worrisome for malignancy but without definitive invasion. "Parafibromin deficient parathyroid tumor" is now used for parathyroid neoplasms that show complete loss of nuclear parafibromin all tumor cells. Newer classification systems are increasingly used in the classification of adult and pediatric adrenal cortical neoplasms. The utility of CYP11B2 immunostain is being increasing reread recognized in the diagnosis of primary unilateral aldosteronism. This update focus on selected complex and significant areas in endocrine pathology that have undergone recent changes.

## 1. Introduction

The diagnostic criteria and classification of endocrine and neuroendocrine tumors is continuously evolving. A variety of updates have been made to the classification of thyroid neoplasms [1]. For example, cribriform morular thyroid carcinoma is no longer considered a subtype of papillary thyroid carcinoma (PTC) but is considered a tumor of unknown histogenesis [2,3]. The invasive encapsulated follicular variant of PTC has genetic alterations and behavior similar to those of follicular thyroid carcinoma and thus is no longer considered a subtype of PTC [3]. Although the terminology becomes confusing, the entity of invasive non-encapsulated follicular variant of PTC remains a subtype of PTC as its underlying genetic alterations and behavior are similar to PTC [3]. Primary thyroid squamous cell carcinoma is now regarded as anaplastic thyroid carcinoma with a squamous cell carcinoma pattern [3,4]. Although mitotic activity and necrosis have been known to be negative prognostic factors in medullary thyroid carcinomas, there is now a grading system for these tumors [5]. Although there are a number of recent changes in the classification of thyroid tumors, the most complicated involves the new category of "high-grade follicular cell derived non anaplastic thyroid carcinoma" which will be discussed in this update.

Increasing understanding of the pathogenesis and germline susceptibility of parathyroid diseases have resulted in significant changes in the diagnosis and classifications. Due to the clonal nature of multiglandular primary parathyroid disease, the terminology of primary parathyroid "hyperplasia" is not used. Rather, primary multiglandular parathyroid disease is now classified under adenomas (multiglandular adenomas/multiglandular parathyroid disease) [6]. The entity of atypical parathyroid tumor has been introduced for parathyroid neoplasm with atypical cytologic and architectural features but lacking unequivocal capsular, vascular, or perineural invasion or invasion into adjacent structures or metastases [6]. The differential diagnosis for this tumor is parathyroid carcinoma-this is not just a parathyroid adenoma with focal fibrosis or a rare mitotic figure. Parafibromin deficient parathyroid neoplasm has also been recently introduced. This is a parathyroid neoplasm (adenoma, atypical parathyroid tumor, or carcinoma) with complete loss of nuclear parafibromin immunoreactivity in all tumor cells indicating bi-allelic somatic or germline *CDC73* inactivation [6].

Although the classic Weiss criteria are still the gold standard for diagnosing adult adrenal cortical tumors, additional classification systems such as the reticulin algorithm and the Helsinki score are being

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increasingly utilized - particularly with tumors (oncocytic and myxoid) that do not classify well with the Weiss system [7,8]. Similarly, although the Wernicke criteria remain the standard for pediatric adrenal cortical neoplasms, a "Modified Wernicke" system, a Helsinki score, and a pediatric Reticulin algorithm have also been proposed. Studies standardizing terminology for primary unilateral aldosteronism to predict clinical outcome continue. Primary multinodular adrenal cortical disease is a clonal-neoplastic process with underlying germline susceptibilities [8].

## 2. Thyroid

### 2.1. *High-grade follicular cell derived non-anaplastic thyroid carcinoma*

"High-grade follicular cell derived non-anaplastic thyroid carcinoma" is a new intermediate category of thyroid carcinoma introduced in the 5th edition of the World Health Organization classification [9–11]. Previously, poorly differentiated thyroid carcinoma (PDC) was the intermediate category between well-differentiated and anaplastic thyroid carcinomas (Fig. 1). Included in this newly designated intermediate category are PDC and differentiated high-grade thyroid carcinoma (Figs. 1 and 2). Differentiated high-grade thyroid carcinomas are differentiated as they retain architectural and/or cytologic features of well-differentiated types of carcinoma of follicular cell derivation (nuclear and/or architecture of PTC, follicular growth pattern of follicular or oncocytic carcinoma) and ≥5 mitoses per 2 $mm^2$ and/or necrosis, with invasion (Fig. 2) [3].

Why was this category added? PDCs include only for tumors with solid, trabecular, or insular (STI) growth with high-grade features (mitosis, necrosis, or convoluted nuclei) per the Turin criteria (Table 1, Fig. 1) [12]. Differentiated high-grade thyroid carcinomas account for tumors that lack the STI growth of PDC but have high-grade features (mitotic activity or necrosis) and are thought to behave similarly to PDC (Fig. 2). Thus, this includes tumors with follicular growth pattern (lacking STI growth) but having high-grade features (≥5 mitoses per 2 $mm^2$ and/or necrosis) (Table 1, Fig. 2). This category also includes PTCs with high-grade features - as PTC was excluded from the Turin criteria (Fig. 2). This category alerts clinicians to clinical significance of thyroid carcinomas with high-grade features.

The Turin PDC criteria require STI growth, absence of PTC nuclei, and at least one of the following: convoluted nuclei or mitoses of ≥3/10 HPF (high power fields) or necrosis (Fig. 1) [12]. As with any system, there are issues with the Turin criteria. Convoluted nuclei are described as small, round hyperchromatic nuclei with nuclear membrane convolutions, smaller and darker than PTC nuclei, irregular convoluted raisin-like contours, only occasional grooves, and loss ground glass appearance [12]. A validation study from Mayo Clinic and the University of Turino found convoluted nuclei to be protective [13]. A study from France found that convoluted nuclei did not have prognostic significance [14]. Additionally, convoluted nuclei were not the sole criteria for any Turin case [12].

Another issue with the Turin criteria concerns the extent of STI growth required for PDC. The WHO suggests the "majority" of the tumor should have STI growth. But there are reports that even a minor STI "component in the presence of high-grade features may affect prognosis". In 2004 Dr. Papotti found tumors to be more aggressive if they had >3/10 HPF, necrosis, age >45 years "irrespective of the extent" of the STI. Interestingly, a comparative study of tumors with high grade features (necrosis & mitoses) regardless of loss of follicular architecture or histological subtype showed a similar prognosis to PDC [14]. Yet, all tumors in this study had trabecular, insular, solid growth (which varied from 5 to 100 %) [14]. But more extensive STI growth was present in PDC compared to differentiated high grade tumors [14].

The original Turin criteria excluded oncocytic tumors from PDCs. A study from the United States and Italy found similar outcome with oncocytic PDCs (75 % oncocytic) and conventional PDCs [13]. A study

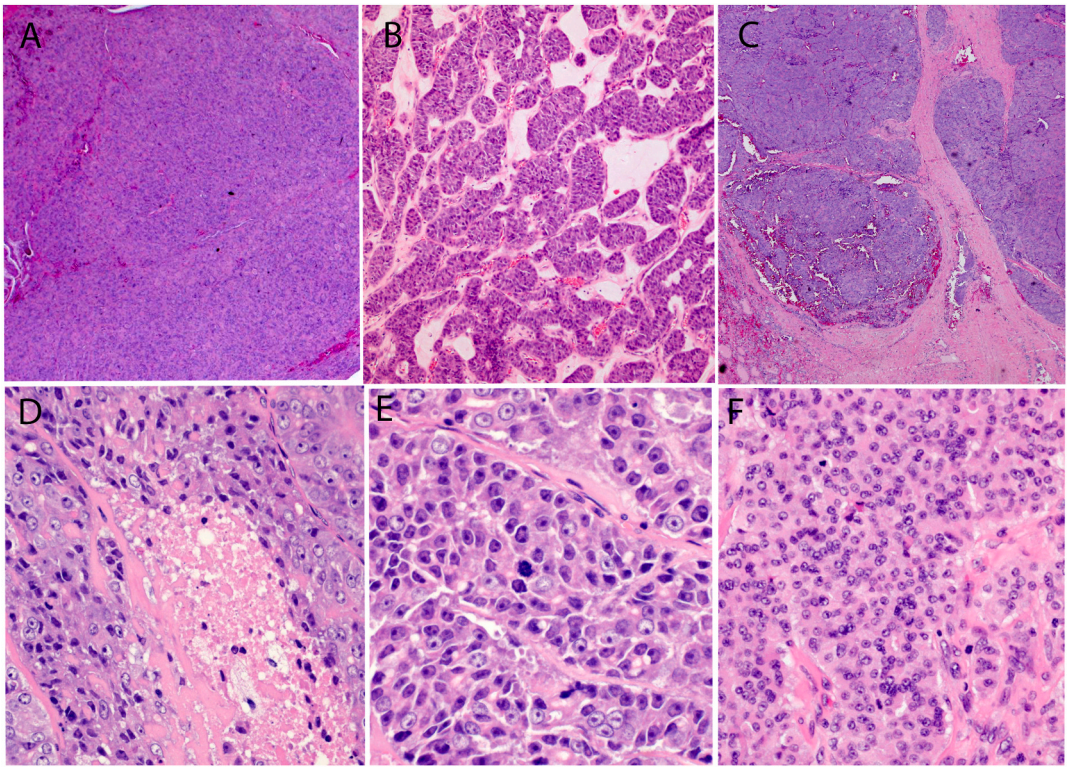


**Fig. 1. Poorly differentiated thyroid carcinoma (PDC).** (A) PDCs have a solid, trabecular, or insular growth pattern. (B) The solid, trabecular, and insular growth pattern is required for a diagnosis of PDC. (C) PDCs are often highly invasive tumors. (D) In addition to a solid, trabecular, or insular growth, PDCs must have necrosis or mitotic activity or convoluted nuclei. (E) Mitotic activity for PDCs must ≥3/10 HPF (2 $mm^2$). (F). Convoluted nuclei can be seen in PDC.

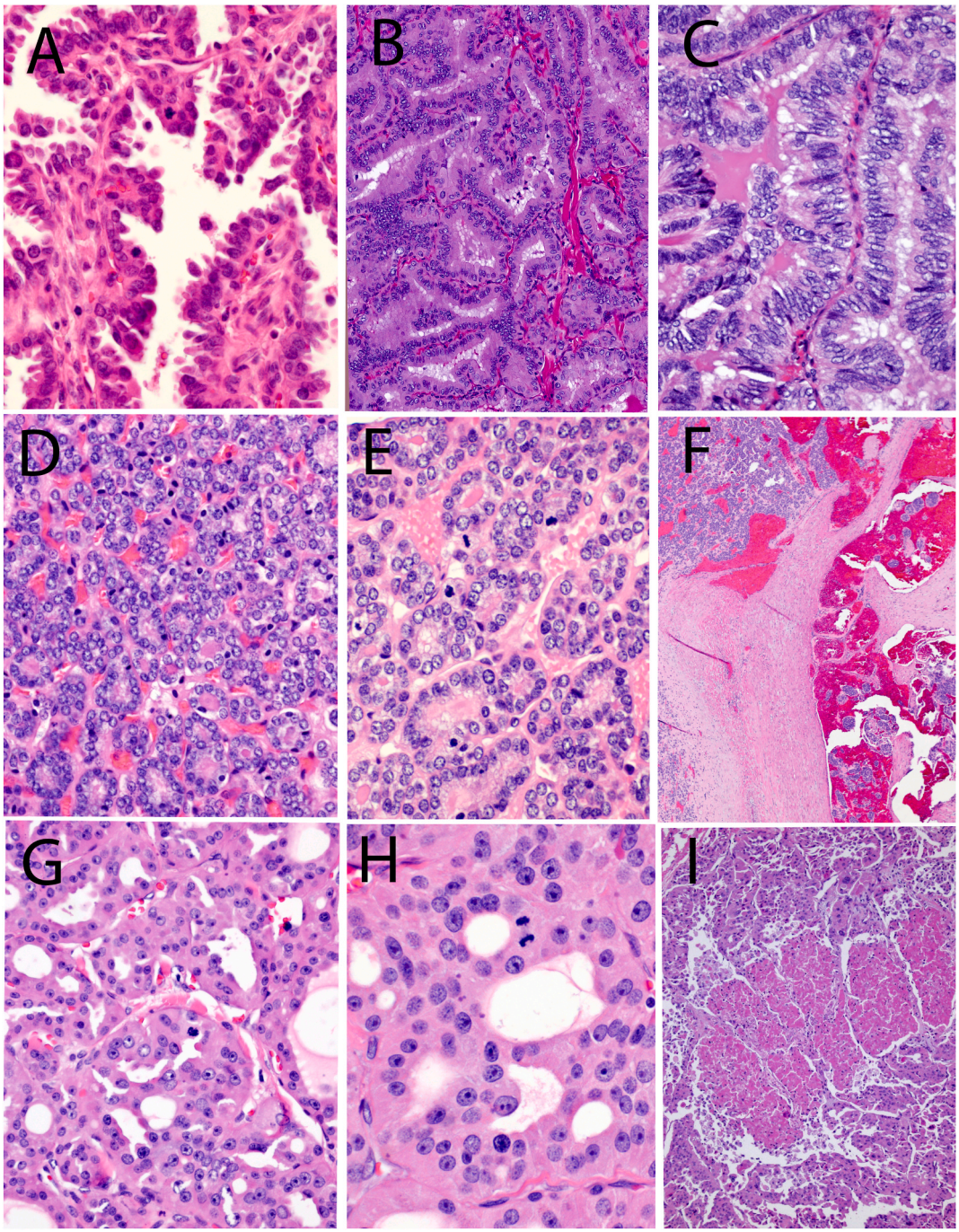


**Fig. 2. Differentiated high-grade follicular cell derived thyroid carcinoma.** (A) Differentiated high-grade papillary thyroid carcinoma (PTC), hobnail subtype. (B): Differentiated high-grade PTC, tall cell subtype. (C): Differentiated high-grade PTC, columnar subtype. (D) Differentiated high-grade follicular thyroid carcinoma. (E) Differentiated high-grade thyroid carcinomas maintain a follicular architecture or papillary pattern, can have PTC nuclei, and have mitotic rate of 5/10 HPF (2 $mm^2$) or necrosis. (F) Differentiated high-grade follicular thyroid carcinomas are often highly invasive tumors. (G) Differentiated high-grade oncocytic thyroid carcinoma maintains its follicular pattern of growth. (H) In addition to maintaining a follicular growth pattern, differentiated high-grade oncocytic thyroid carcinoma much have mitotic rate of 5/10 HPF (2 $mm^2$) or necrosis. (I) Oncocytic thyroid carcinomas often have a solid growth pattern as is seen in this tumor. Thus, a solid/trabecular/insular growth pattern in an oncocytic tumor with high-grade features (increased mitotic activity or necrosis) is diagnosed as poorly differentiated thyroid carcinoma, oncocytic type.

from France also found no prognostic difference between the oncocytic and conventional PDCs [14]. However, a study by Dr. Papotti's group in 2004 included 66 PDCs with oncocytic features. Dr. Papotti's group found oncocytic PDCs had lower disease specific survival than classic PDCs [15]. Dr. Bartlett's group also found oncocytic PDCs to have worse outcomes than conventional PDCs [16]. Thus, oncocytic thyroid carcinomas with STI growth and high-grade features are now considered a type of PDC. In a study from Memorial Sloan Kettering Cancer Center and Emory University of 210 PDCs, 39 % had an oncocytic component and 25 % met the WHO oncocytic cutoff of 75 %. By multifactorial analysis any oncocytic component in the tumor was associated with decreased disease specific survival and increased radioactive iodine refractoriness; and tumors with >25 % oncocytic had increased locoregional recurrence [17]. Oncocytic carcinomas without STI

**Table 1**
High-grade follicular cell derived non-anaplastic thyroid carcinoma.

| Poorly Differentiated Thyroid Carcinoma | Differentiated High-Grade Thyroid Carcinoma |
|---|---|
| ***Solid/trabecular/insular*** growth in a tumor diagnosed malignant based on invasion | Retain architectural &/or cytologic features of well-differentiated carcinoma of follicular cells (papillary, follicular, or oncocytic) |
| ***Absence of PTC nuclear features*** At least 1: mitoses $\geq$ ***3*** per 2 $mm^2$, necrosis, or convoluted nuclei | ***Has follicular architecture or PTC nuclei*** Has mitoses $\geq$ ***5*** per 2 $mm^2$ or necrosis |
| Both retain immunophenotype of follicular cells and lack anaplastic morphology | |

architecture but with mitotic activity or necrosis are classified as differentiated high-grade oncocytic carcinomas, and oncocytic carcinomas with STI architecture and mitotic activity or necrosis are classified as poorly differentiated oncocytic carcinomas.

The Turin criteria excluded tumors with PTC nuclei. According to the Turin paper, aggressive PTC variants (tall cell, columnar) and PTC with "high mitotic activity and/or necrosis ought not be included into the PD carcinoma category despite the fact that they may represent high-grade neoplasms."(12) Thus, it is known that aggressive subtypes of PTC and PTCs with high mitotic activity and/or necrosis are high-grade neoplasms. For example, the hobnail subtype of PTC was even described as "A New Aggressive Variant of Moderately Differentiated Papillary Carcinoma" [18]. Although these high grade PTCs are still excluded from the Turin criteria for PDC due to the PTC-type nuclei, PTCs are included in this new intermediate category and classified as differentiated high-grade PTCs.

Many studies find the prognosis of differentiated high-grade thyroid carcinomas to be similar to that of PDCs [14,19]. Dr. Ghossein's group studied 164 high-grade differentiated thyroid carcinomas and 200 PDCs (meeting the Turin criteria) and found the high-grade differentiated carcinomas to be less radioactive iodine avid and to have higher rates of lymph node metastases but fewer distant metastases than PDCs [19]. Additionally, 95 % of the differentiated high-grade carcinomas were high-grade PTCs - which are generally BRAF V600E predominant tumors whereas PDCs are generally RAS-predominant tumors [19].

Recent studies suggest caveats regarding the prognosis of high-grade follicular cell derived non-anaplastic thyroid carcinomas. Prior studies had shown differentiated high-grade follicular cell derived thyroid neoplasms had similar prognosis as PDCs. Dr. Barletta's group compared 15 PTCs with high-grade features (5/10 HPF +/or necrosis) including 5 columnar, 2 tall cell, 2 hobnail, 1 solid, 1 classic, and 4 mixed PTCs with 47 PDCs [20]. The differentiated high-grade PTCs had more aggressive clinicopathologic features and worse 2 year (44 % vs 84 %) and 5-year (67 % vs 84 %) disease free survivals than the PDCs [20]. Importantly, Dr. Bartletta also compared the high-grade PTCs with PDCs that were grossly invasive, often with extensive vascular invasion, and the differentiated high-grade PTCs had decreased disease specific survival compared to the grossly invasive PDCs [20]. In another study, Dr. Barletta's group evaluated the extent of invasion in PDCs and found PDCs with focal capsular or focal vascular invasion had an excellent prognosis, while those with extensive vascular invasion or widely invasive tumors had a worse outcome [16]. Thus, it is helpful to specify these features in pathology reports. Also, as noted previously oncocytic PDCs may be more aggressive than conventional PDCs [15]. Although PDCs and differentiated high-grade thyroid carcinomas may both be in the intermediate category of "High-Grade Follicular Cell-Derived Non-Anaplastic Thyroid Carcinoma" and are thought to have a generally similar clinical outcome, there are additional prognostic factors to consider even among the tumors in these categories.

## 3. Parathyroid

### 3.1. Multiglandular parathyroid disease

Significant changes in diagnostic pathology of the parathyroid gland include the recognition of primary multiglandular parathyroid disease to be a clonal disorder with multiple adenomas, and thus the term "hyperplasia" is no longer used for this group. This is now regarded as primary multiglandular parathyroid disease or as multiple adenomas. At this time, secondary parathyroid disease (such as from chronic renal failure) is still regarded as hyperplasia.

### 3.2. Atypical parathyroid tumor

Another significant change is the new entity "atypical parathyroid tumor". This designation is used for a parathyroid neoplasm with atypical cytologic and architectural features, but lacks unequivocal capsular, vascular, or perineural invasion or invasion into adjacent structures or metastases (Fig. 3) [6]. These are usually sporadic tumors but can occur as part of inherited hyperparathyroidism. They usually lack a palpable mass and have an elevated serum calcium between that of an adenoma and a carcinoma. These tumors are usually cured by resection but recurrent and persistent disease occur in some cases, so follow-up is recommended. Focal fibrosis and occasional mitoses are insufficient for diagnosis of atypical parathyroid tumor. Importantly, the differential diagnosis of atypical parathyroid tumor is with carcinoma (not adenoma) (Table 2, Fig. 3) [6].

### 3.3. Parafibromin deficient parathyroid tumor

Parafibromin deficient parathyroid tumor is a parathyroid neoplasm (adenoma, atypical parathyroid tumor, or carcinoma) with complete loss of nuclear parafibromin immunoreactivity in all tumor cells (Fig. 3) [6]. This finding indicates bi-allelic somatic or germline *CDC73* inactivation. *CDC73* (1q21-q32) is a member of the human RNA polymerase II -associated factor complex involved in DNA transcription [6,21–24]. Inactivating *CDC73* mutation result in decreased nuclear parafibromin and up-regulation *CCND1*/cyclin D1 and c-myc mRNA resulting in cell cycle progression and inhibition of apoptosis [6,21–24]. Thus, individuals with bi-allelic somatic or germline *CDC73* inactivation have loss of nuclear parafibromin expression in their parathyroid adenomas and carcinomas [21–24]. A caveat is the rare occurrence of preserved nuclear parafibromin expression if the *CDC73* inactivation is due to missense rather than truncating single nucleotide variants. Thus parafibromin expression does not completely exclude *CDC73* inactivation. Additionally, nucleolar loss of parafibromin is considered abnormal and requires molecular testing to confirm its significance [6,25].

Adenomas retain nuclear parafibromin expression unless they are in the setting of germline *CDC73* alteration such as in hyperparathyroidism jaw tumor syndrome or familial isolated hyperparathyroidism (Fig. 3) [6,24,26,27]. Thus, sporadic adenomas are not associated with loss of nuclear parafibromin expression. Parathyroid carcinomas are rare tumors but occur in approximately 15 % of individuals with hyperparathyroidism jaw tumor syndrome, and tumors in the setting of germline *CDC73* inactivation show loss of parafibromin [6].

Somatic *CDC73* alterations are generally not seen in sporadic adenomas, but they can occur in sporadic parathyroid carcinomas (Fig. 3) [24,26]. In addition to somatic CDC73 alteration in some sporadic parathyroid carcinomas, up to 30 % of apparently sporadic parathyroid carcinomas are found to have germline *CDC73* inactivation [6]. Thus, individuals diagnosed with parathyroid carcinoma are offered germline genetic testing. Germline genetic testing may be considered in individuals with primary parathyroid disease <45 years of age, those with recurrent primary hyperparathyroidism, primary multiglandular parathyroid disease, a family history of or components of an inherited syndrome, loss of p27, menin or max or multiple nodular proliferations in

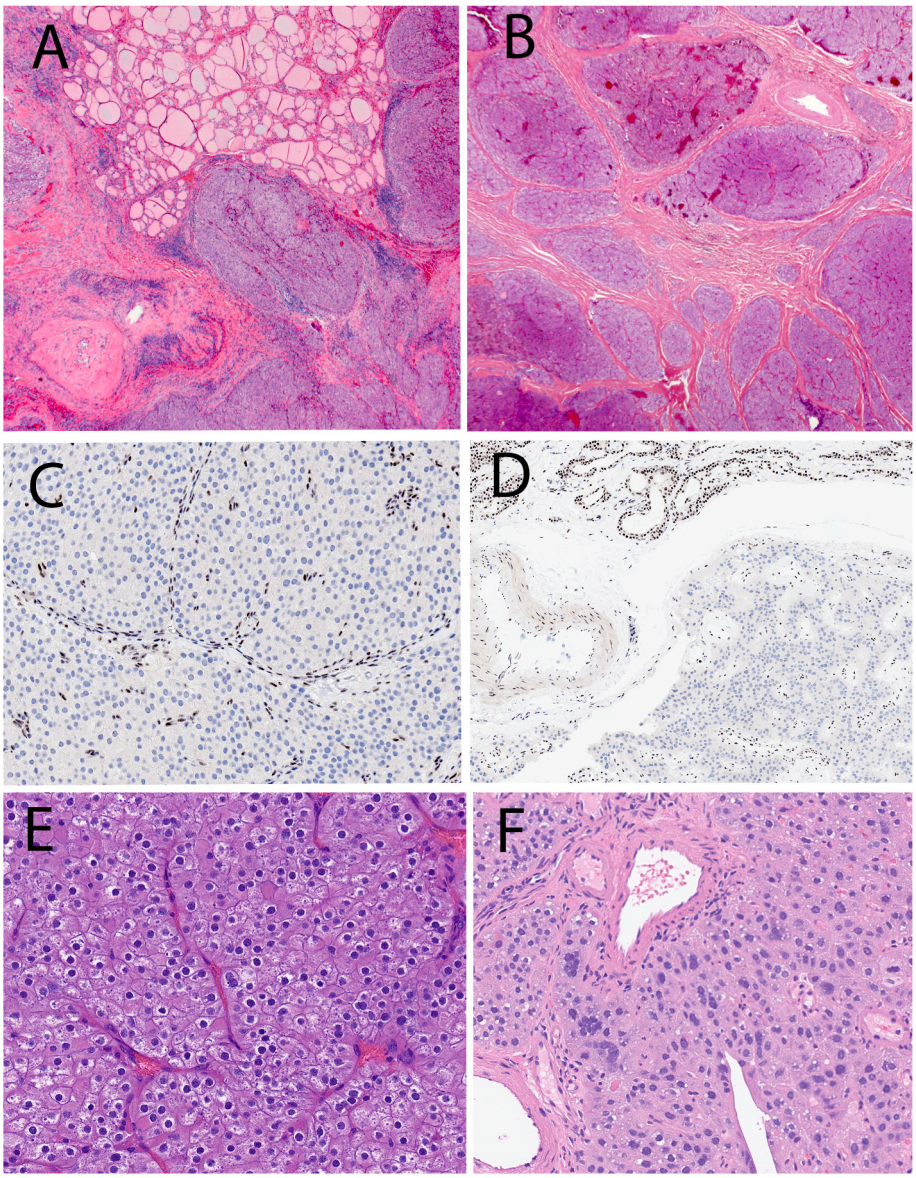


**Fig. 3. Parathyroid disease**. (A) This parathyroid carcinoma shows invasion into the thyroid. Invasive growth or metastases are required for diagnosis of parathyroid carcinoma. (B) this tumor shows a very irregular growth pattern, with solid nests of cells that are fairly monotonous. These are worrisome features, but without definitive invasion would be regarded as an atypical parathyroid tumor. In a case like this extensive sampling is needed. (C). This is a parathyroid carcinoma with complete nuclear loss of parafibromin immunostaining throughout all of the tumor cells. It is important to note the internal positive control of endothelial cells. Not all parathyroid carcinomas show loss of parafibromin. (D) This is a parathyroid adenoma occurring in the setting of an underlying germline *CDC73* alteration. The "rim" has retained parafibromin but the adenoma shows loss of parafibromin. Loss of parafibromin can be seen with underlying *CDC73* alteration. Otherwise, loss of parafibromin is generally is not seen in sporadic adenomas. (E) This parathyroid tumor shows sheet like growth of cells with eosinophilic cytoplasm, nuclear enlargement, and perinuclear halos which are histologic features suggestive of underlying *CDC73* inactivation. (F) Multinucleate cells are also suggestive of underlying *CDC73* inactivation.

**Table 2**
Tips when considering a diagnosis of atypical parathyroid tumor.

- Conventional parathyroid adenomas can show fibrosis (large, FNA, or cystic), thus focal fibrosis is insufficient for diagnosis of atypical parathyroid tumor.
- Occasional mitoses can be seen in any benign parathyroid tumor and are insufficient for diagnosis of atypical parathyroid tumor.
- The term atypical parathyroid tumor is reserved for a tumor with atypical features whose differential diagnosis carcinoma.
- Parathyroid carcinomas often have a Ki67 > 5 %, adenomas much lower, atypical parathyroid tumors have intermediate proliferative index.
- Mitoses >5/50 hpf (10 $mm^2$), necrosis, macronucleoli, atypical mitoses, or Ki-67 > 5 % are highly worrisome for malignancy and indicate the need for extensive sampling of the tumor to rule out invasion.
- The diagnosis of parathyroid carcinoma requires invasive growth or metastasis.

parathyroid, morphologic features suggesting *CDC73* inactivation, parafibromin deficient tumors, and parathyroid carcinomas (regardless of parafibromin status as 30 % of apparently sporadic carcinomas have germline *CDC73* inactivation) [6]. Whole genome or whole exome sequencing can be performed, but a select genetic panel or targeted gene testing may be done due to accessibility and cost.

Histologically, there are genotype-phenotype correlations for underlying *CDC73* inactivation. Sheet like growth (rather than acinar), eosinophilic cytoplasm, nuclear enlargement, coarse chromatin, perinuclear clearing with a "koilocyte-like" appearance, binucleated and multinucleate cells, arborizing vasculature and often a thick capsule are histologic clues to underlying *CDC73* inactivation (Fig. 3) [28].

### 3.4. Biomarkers in parathyroid disease

Ki-67 and parafibromin are the main biomarkers utilized in diagnostic parathyroid pathology, but many immunostains may be useful in the diagnosis of parathyroid neoplasms [6,27,29]. Interestingly, although parathyroid tissues and tumors are positive for chromogranin-A, they are often negative for synaptophysin [6,29]. Furthermore, monoclonal PAX8 antibodies are negative in parathyroid, while unsuspecting pathologists may order a PAX8 immunostain and not

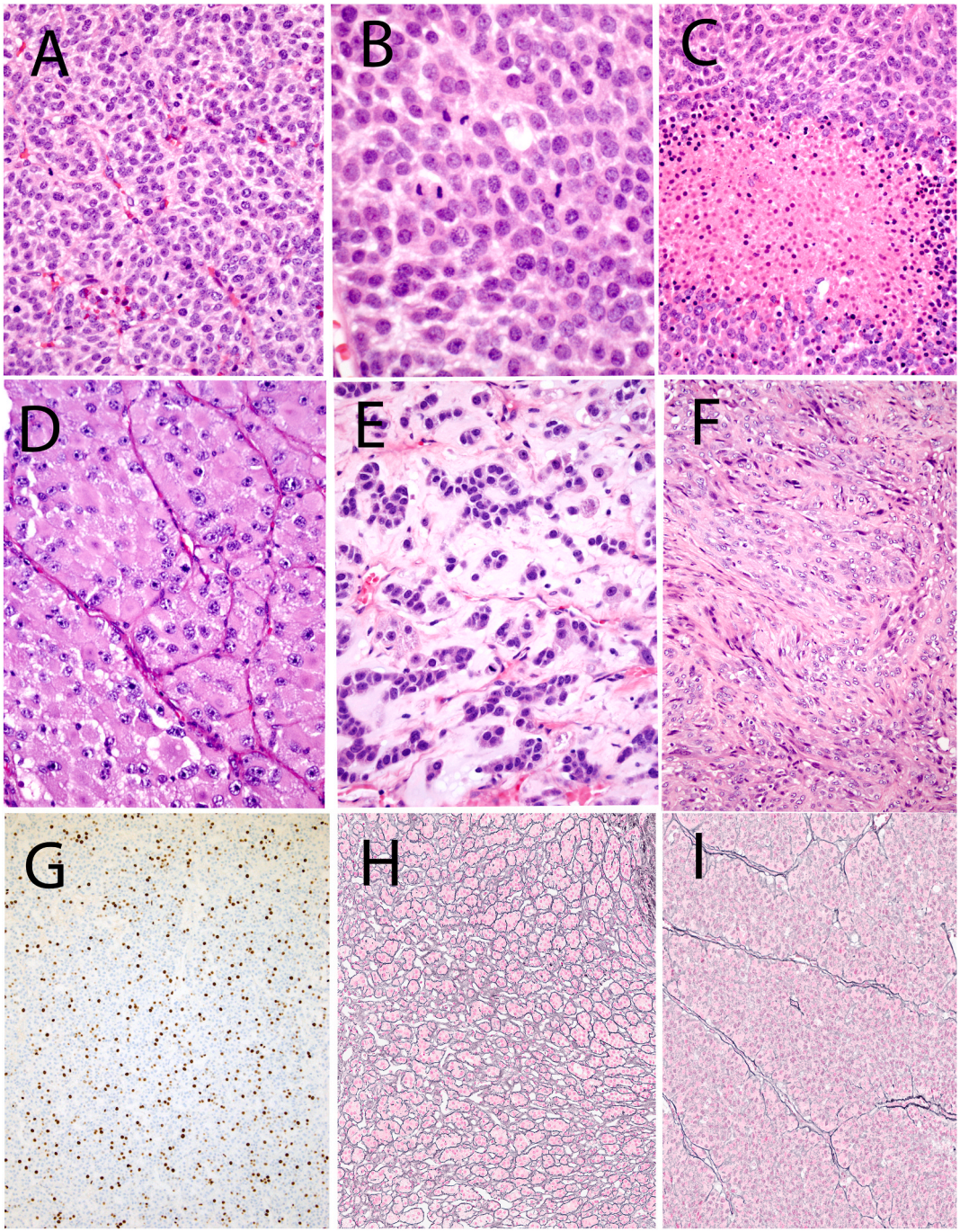


**Fig. 4. Adrenal cortical carcinoma (ACC).** (A) ACCs often have a solid growth pattern but they can have a trabecular/insular type growth pattern as well. (B) Numerous mitotic figures are seen in this ACC. (C) necrosis is present in this ACC. (D) Oncocytic ACC with mitotic activity. Adrenal cortical tumors must be 90 % oncocytic to be regarded as oncocytic adrenal cortical neoplasms. (E) Myxoid ACC can not be classified reliably by standard Weiss criteria. (F) Sarcomatoid ACCs are difficult to diagnose and often require a panel of immunostains and clinical and radiographic correlation. (G) Proliferative activity, mitotic activity and Ki-67 as shown in this image, are central to the evaluation of adrenal cortical neoplasms. ACCs in adults generally have a a proliferative index of >5 %. (H) This is an intact reticulin staining pattern in an adrenal cortical adenoma. (I) Loss of reticulin staining is seen in addition to high-grade features in ACC.

realize which actual biomarker they are interpreting as the polyclonal PAX8 immunostains are very nonspecific [30]. For distinguishing benign from malignant parathyroid tumors, other than Ki-67 and parafibromin, additional biomarkers are not commonly used in daily diagnostic practice. For example, parathyroid carcinomas are often positive for PGP9.5, galectin3, and hTERT, show p53 overexpression and loss of parafibromin, E-cadherin, p27, Bcl2a, mdm2, Rb, and 5hmC [6,29,31]. Parathyroid adenomas often show the opposite staining pattern to that of carcinomas with these biomarkers showing retained parafibromin and positive staining for cyclin D1, BCL 2, p27, and RB with lack of staining for PGP 9.5 and galectin 3 [6,29,31].

## 4. Adrenal gland

### 4.1. Distinguishing adrenal cortical carcinoma from other malignancies

The diagnosis of adrenal cortical carcinomas is often straightforward (Fig. 4). With clearly malignant adrenal cortical carcinomas (ACCs) the issue is not if it is malignant but rather whether it is an ACC or a metastasis to the adrenal gland or a primary adrenal sarcoma or other tumor. In this setting, immunostains can be help classify the malignancy. As metastases to the adrenal gland are more common than ACCs, a panel of immunostains is utilized (Table 3). Adrenal cortical tumors usually show some keratin (AE1 AE3 and cam 5.2) staining, but very poorly differentiated ACCs may be negative or show only focal keratin expression [8,32]. Sarcomatoid ACCs may necessitate correlation with clinical and radiographic features as well as a panel of immunostains (Fig. 4) [33]. Importantly, pheochromocytomas (intra-adrenal paragangliomas) are negative for keratin. This is also helpful as metastases of neuroendocrine carcinomas to the adrenal gland are positive for neuroendocrine markers chromogranin-A and synaptophysin, similar to pheochromocytomas, but they are also positive for keratin [8,32]. A pitfall in using neuroendocrine markers in the adrenal gland is that cortical tissue and tumors are positive for synaptophysin (but negative for chromogranin-A) [8,32]. Another pitfall is adrenal cortical positivity for Melan-A/Mart 1. As metastatic melanoma to the adrenal is not uncommon, additional biomarkers such as SOX10, S100, etc. are helpful in separating ACC from metastatic melanoma [8]. Although steroidogenic factor 1 (SF1) is positive in any steroidogenic tumor, it is one of the best biomarkers commonly utilized to identify adrenal cortical tissues in tumors [8,32]. Inhibin-α is also positive in steroidogenic tumors, but it is only positive in functional adrenal cortical tumors and may also be up regulated in some paragangliomas and neuroendocrine tumors [34]. Although primary adrenal gland mesenchymal tumors are rare, angiosarcoma is the most common primary sarcoma of any endocrine organ. Angiosarcomas in endocrine organs are invariably epithelioid and keratin positive [35]. Thus, in difficult cases, vascular markers such as ERG and CD31 may be helpful in identifying these tumors [35].

### 4.2. Algorithms for diagnosing adrenal cortical tumors

It is at the low end of the spectrum of adrenal cortical tumors that most diagnostic challenges arise. Numerous classification systems have and continue to be proposed [8,32,36]. The Weiss criteria of 1984 updated in 1989 (Table 4) remain the gold standard for the diagnosis of ACC in adults [7,8,36–38]. Additional algorithms are increasingly utilized including the Reticulin algorithm and the Helsinki score. The Reticulin algorithm and the Helsinki score may be used in the diagnosis of conventional ACCs as well as oncocytic and myxoid adrenal cortical tumors for which the conventional Weiss criteria may not be applicable (Table 4, Fig. 4) [7,39–44]. The Weiss system for adult ACCs includes 9 criteria, in the presence of 3 or more criteria in a tumor correlates with malignancy (Table 4) [38]. Although no single feature is diagnostic of malignancy, mitotic rate greater than 5/50 high-power fields (10 mm2), atypical mitoses, and venous invasion were most significant [37]. From the Weiss system (1989), ACCs with >20 mitoses per 50 HPF (10 mm2) are high-grade (median survival 14 months), and those with less are considered low-grade ACCs (median survival 58 months) [38].

Common to all classification systems is mitotic activity and/or proliferative index by Ki-67 (MIB-1) immunostain (Fig. 4) [8,32,36,38,39,45,46]. Although ACCs with >20 mitoses per 50 HPF (10 mm2) are graded as high-grade and <20 as low, mitotic activity and Ki-67 indices are continuous variables. For adults, a Ki-67 index of >5 % is quite sensitive and specific for malignancy. Digital analysis is recommended to assess Ki-67 proliferative indices due to increased reproducibility and reliability and decreased variation [47].

The "Helsinki score" was proposed in 2015 as a predictive model for metastasis in ACCs [48]. The score is calculated by 3 points for mitotic rate greater than 5/50 HPF (10 mm2), 5 points for necrosis, and adding the proliferative index by Ki-67 computer image analysis in the most proliferative area of the tumor (Table 4). A cutoff of 8.5 had 100 % sensitivity and 99.4 % specificity for diagnosing metastatic ACC [48]. A validation study of 225 ACCs found both Helsinki score and Weiss criteria to be predictors of poor prognosis, and found a Helsinki threshold of 28.5 % and Ki-67 of 20.5 % as the best predictors of death from disease [41].

After the Weiss criteria, the most highly utilized classification system is the "Reticulin algorithm" [39,40,49]. Reticulin histochemical staining

**Table 3**
Distinguishing adrenal cortical carcinoma from metastases and other tumors.

| | Adrenal cortical carcinoma[a] | Metastatic carcinoma | Metastatic NET/NEC[b] | Metastatic melanoma | Pheo[c] |
|---|---|---|---|---|---|
| **Chromogranin-A** | − | − | + | − | + |
| **Synaptophysin** | + | − | + | − | + |
| **Keratin (AE1/AE3, Cam5.2)** | +/− | + | + | − | − |
| **Steroidogenic factor-1 (SF1)** | + | − | −/+ | − | −/+ |
| **Inhibin-α** | +/− | − | − | − | − |
| **Mart1/MelanA** | + | − | − | + | − |
| **SOX10 and S100** | − | − | − | + | − |
| **CAVEATS** | | | | | |

- ACCs are often positive for synaptophysin, but negative for chromogranin-A distinguishing them from pheochromocytomas and NET/NEC.
- ACCs, particularly poorly differentiated tumors, may not show staining for keratin or may have only focal staining.
- ACCs are positive for Mart1/Melan-A, but are negative for SOX10 and S100 which is helpful to distinguish them from metastatic melanoma.
- Nonfunctional ACCs are usually negative for inhibin-α.
- SF1 & inhibin-α are positive in any steroidogenic tumor.
- Inhibin-α can show staining in some paragangliomas and neuroendocrine tumors.
- Metastatic carcinoma, such as from breast, can show SOX10 and S100 staining.

[a] ACC: adrenal cortical carcinoma.
[b] NET/NEC: neuroendocrine tumor/neuroendocrine carcinoma.
[c] Pheo: pheochromocytoma.

**Table 4**
Algorithms for diagnosing conventional adrenal cortical carcinoma in adults.

| |
|---|
| ***Weiss Criteria*** |
| • Nuclear grade (Fuhrman/USP grade III or IV)<br>• Mitotic rate >5/50 HPF<br>• Atypical mitotic figures<br>• Clear cells comprise ≤25% of the tumor<br>• Diffuse architecture in >1/3 of tumor<br>• Necrosis<br>• Venous invasion<br>• Sinusoid invasion<br>• Capsular invasion<br>≥3 criteria correlates with malignancy |
| ***Reticulin Algorithm*** |
| **Reticulin Network Disruption**<br>***AND*** *(1 of the following):*<br>• Mitoses >5/50 HPF<br>• Necrosis<br>• Vascular invasion |
| ***Helsinki Score (Predict Metastases in Adrenal Cortical Tumors)*** |
| 3 points for ( mitotic rate >5/50 HPF) + 5 points for necrosis + proliferation index in the most proliferative area of the tumor |

is used to evaluate for disruption of the reticulin network. For an adrenal cortical tumor to be classified malignant, the algorithm requires reticulin network disruption and one additional feature (mitotic rate >5/50 HPF (10 mm2), or necrosis, or vascular invasion) (Table 4, Fig. 4) [39,40,49]. The main drawback of this system is the requirement of having a very good reticulin stain.

### 4.3. Diagnosing special types of adrenal cortical carcinoma

There are caveats to the diagnosis of adrenal cortical tumors that are >90 % oncocytic, myxoid, or occurring in children (Table 5) [36]. A tumor must be >90 % oncocytic to be regarded as an oncocytic adrenal cortical neoplasm [50]. Oncocytic neoplasms may be over-diagnosed as malignant by standard Weiss criteria. Based on studies by Dr. Lin, Dr. Weiss and Dr. Bisceglia, the "Lin-Weiss-Bisceglia" system was developed to classify oncocytic adrenal cortical neoplasms [38,50–52]. One major criteria (high mitotic rate, atypical mitoses, or vascular invasion) is required for diagnosis of malignancy. One to 4 minor criteria (size >10 cm or weight >200 g, necrosis, capsular invasion, or sinusoidal invasion) indicate uncertain malignant potential. If no major or minor criteria are present, the tumor is regarded as benign [50,51]. The Reticulin algorithm is helpful in the evaluation of oncocytic adrenal tumors [39,40,42,49,53,54]. The Helsinki score (≥19 vs < 13) may also help predict malignant behavior of oncocytic tumors [41].

The behavior of myxoid adrenal cortical tumors cannot be predicted with Weiss criteria [55]. In a study of 10 tumors with prominent myxoid change, a fatal outcome occurred with a tumor with a Weiss score of 1 [55]. If a myxoid cortical tumor meets Weiss criteria for malignancy then it is reasonable to diagnose the tumor malignant. But if a tumor does not meet those criteria, the tumor should not be diagnosed benign based on Weiss criteria alone. The Reticulin algorithm is proving to be helpful in the evaluation of these tumors, and the Helsinki score might also have some prognostic significance (Table 5) [40,41,53,56].

The standard Wieneke criteria for pediatric adrenal cortical neoplasms has 9 features (tumor weight >400 g, size >10.5 cm, vena cava invasion, capsular invasion, vascular invasion, necrosis, extension into periadrenal soft tissue or adjacent organs, mitoses >15/20 HPF, and atypical mitosis) (Table 5) [57]. The presence of ≥4 criteria portends poor outcome; 3 indeterminate malignancy; and ≤2 benign [57]. Although the Wieneke system remains the standard for pediatric tumors, more recent systems have been proposed [44,56,58,59]. The "Modified Wieneke" system has 5 parameters (necrosis, capsular invasion, venous invasion, mitoses >15/20 high-power fields, and Ki-67 > 5 %), and tumors with ≥2 have a worse prognosis [58]. A cutoff of 24 points in the Helsinki score is helpful in pediatric tumors (Table 5) [56]. A pediatric Reticulin algorithm requiring reticulin network disruption and 1 of 3 features (mitoses >15/20 HPF, necrosis, or vascular invasion) is helpful in pediatric tumors [44]. In adult neoplasms >5 mitoses per 50 HPF (10mm2) or Ki-67 > 5 % is quite sensitive and specific for malignancy, but in children the mitotic cutoff in the Wieneke system, Modified Wieneke system, and pediatric Reticulin algorithm is > 15/20 HPFs (Table 5) [44,56–59]. In the Modified Wieneke system, no tumor with a Ki-67 of <15 % had recurrence or metastasis [58]. In another pediatric study, Ki-67 ≥ 15 % was associated with poor outcome, and Ki-67 of <10 % was seen in benign tumors [59]. Comparing the classic Wieneke criteria, Helsinki score (cutoff 24), Reticulin algorithm, and Ki-67 labeling index, all 3 systems and Ki-67 > 18 % had similar sensitivity of ≥80 % and specificity of 63–81 % in pediatric tumors [56].

Although Ki-67 is the most helpful in and widely used biomarker in the evaluation of adrenal cortical tumors, IGF2, β-catenin, and p53 have shown utility [8,46,60–62]. IGF2 may help distinguish ACC from adenoma, particularly with a Golgi/juxtanuclear staining pattern [60,63–65]. *β*-catenin expression (nuclear or cytoplasmic) reflecting WNT/*β*-catenin pathway activation, usually due to *CTNNB1* alteration,

**Table 5**
Diagnosing special types of adrenal cortical carcinoma.

| | |
|---|---|
| **Oncocytic*** | ***Lin-Weiss-Bisceglia System***<br>**Major Criteria**<br>• High mitotic rate<br>• Atypical mitoses<br>• Vascular invasion<br>1 major malignant; 1-4 minor uncertain malignant potential ; No major/minor benign<br>**Minor Criteria**<br>• *Size >10cm or weight >200g*<br>• Necrosis<br>• Capsular invasion<br>• Sinusoidal invasion<br>***Reticulin Algorithm and Helsinki Score may also be used** |
| **Myxoid*** | • Tumors that are predominantly myxoid do not classify well with Weiss criteria<br>***Reticulin Algorithm and Helsinki Score may also be used** |
| **Pediatric** | ***Wieneke Criteria***<br>• Tumor weight >400g<br>• Tumor size >10.5 cm<br>• Vena cava invasion<br>• Capsular invasion<br>• Vascular invasion<br>• Necrosis<br>• Extension into periadrenal soft tissue or adjacent organs<br>• >15 mitoses/20 HPF<br>≤2: benign; 3: indeterminate; ≥4: portends poor clinical outcome |
| | ***Modified Wieneke***<br>• Necrosis<br>• Capsular invasion<br>• Venous invasion<br>• Mitoses >15/20 HPF<br>• Ki67 >15%<br>>2 poor prognosis |
| | ***Pediatric Reticulin Algorithm***<br>• Reticulin network disruption<br>• *AND:* mitoses >15/20 HPF *OR* necrosis *OR* vascular invasion |
| | ***Helsinki*** (cutoff 24 points) |

portends decreased survival in ACCs [61]. Aberrant overexpression (rarely loss) of p53 occurs in most pediatric tumors reflecting germline *TP53* alteration, and somatic or germline alterations occur in 20–30 % of adult ACCs [61,62]. These immunostains, IGF2, B-catenin, and p53, reflect the main genetic pathways that are altered in the pathogenesis of ACC [8].

### 4.4. Primary unilateral aldosteronism

Interestingly, aldosterone producing adrenal cortical disease is rarely associated with malignancy (unlike sex-steroids) [8]. The most pressing current topic regarding adrenal cortical aldosterone production is predicting clinical outcomes with histologic and immunohistochemical (CYP11B2, aldosterone synthase) staining patterns in primary unilateral aldosteronism [8,66–75]. CYP11B2 may be helpful in identifying sites of aldosterone production, distinguishing non-functioning from aldosterone producing adenomas (APA), and may predict biochemical response, but predicting complete clinical response is more difficult [66–75]. The International Histopathology Consensus for Unilateral Primary Aldosteronism (HISTALDO) classification was proposed to standardize the nomenclature of areas of aldosterone production with CYP11B2 in unilateral aldosteronism [68]. This classification includes the rare aldosterone producing ACC, APA (circumscribed CYP11B2 positive solitary neoplasm $\geq$10 mm), aldosterone producing nodule (APN, CYP11B2 positive $<$10 mm lesion visible on H&E), aldosterone producing micronodule (APM, previously known as aldosterone producing cell clusters, CYP11B2 positive $<$10 mm lesion of zona glomerulosa cells beneath capsule that do not differ from adjacent cortical cells on H&E), multiple APNs/APMs (MAPN/MAPM), and aldosterone producing diffuse hyperplasia (relatively broad uninterrupted strip of zona glomerulosa with $>$50 % CYP11B2 positive cells) [68].

They proposed classical and non-classical histologic patterns. The classic pattern is single APA or APN, and they noted that the non-tumorous adrenal cortex adjacent to the lesion often had “paradoxical ZG hyperplasia with negative CYP11B2 immunostaining, APMs or APNs or aldosterone-producing diffuse hyperplasia.”(69) These definitions showed some differences in biochemical success, but no difference in clinical outcome [68]. Some, although not all, subsequent studies utilizing the HISTALDO classification also found differences in biochemical success between classic and non-classic cases yet complete clinical

success is more difficult to predict [66–73,76–80]. A Swedish study suggests "HISTALDO may over-report non-classical histology" [81]. The Swedish study incorporated a B2 ratio (size ratio of the largest to second-largest CYP11B2 positive nodule) in cases with multiple nodules. A B2 ratio cutoff ≥8.1 %, reclassified 29 of 55 non-classic cases. Higher B2 ratios correlated with complete clinical response and fewer antihypertensive medications postoperatively [81]. Thus, progress continues to be made in classification of primary unilateral aldosteronism. For pathologists not familiar with the CYP11B2 staining pattern of normal adrenal glands, van de Wiel et al. (2022) provides excellent illustrations of CYP11B2 staining with age [82].

### 4.5. Multinodular adrenal cortical disease

Although the term "hyperplasia" is only used for congenital adrenal hyperplasia and pituitary or ectopic ACTH driven adrenal disease, it is no longer used for primary multinodular adrenal cortical disease due to its clonal nature reflecting underlying germline alterations [8,83].

Although sporadic nodular adrenal cortical disease is a diagnostic category, it is unlike the rest as this represents a (possibly few) small (<1 cm) incidental, usually unilateral, nonfunctional nodule(s) (Table 6). Rather, the terminology nodular adrenal cortical disease generally refers to primary adrenal cortical nodules causing endogenous Cushing syndrome with underlying germline alterations (Table 6) [8,83]. Bilateral micronodular (<1 cm) adrenal cortical disease usually affects children and young adults with underlying germline variants activating the protein kinase A pathway. Bilateral micronodular disease includes primary pigmented nodular adrenal cortical disease (PPNAD) which can occur in Carney complex (c-PPNAD) or without Carney complex (i-PPNAD) – although both have germline *PRKAR1A* alterations [8,83]. The adrenal glands have multiple pigmented nodules and internodular atrophy. Another type of bilateral micronodular disease is isolated micronodular adrenal cortical disease (i-MAD) characterized by multiple non-pigmented micronodules and germline alterations of *PRKACA*, *PDE8B*, or *PDE11A* [8,83]. Bilateral macronodular adrenal cortical disease has multiple, bilateral nodules >1 cm, and usually occurs in adults (Table 6) [83,84]. About 5 % are syndromic with underlying *MEN1*, *APC*, *GNAS*, or *FH* alterations, but non-syndromic forms are increasingly recognized as a genetic disease particularly with *ARMC5* which can have >100 alterations and *KDM1A* in food dependent Cushing [84,85]. Primary aldosteronism can also have with multiple bilateral nodules, and may be more common than expected [86]. Although there are some histologic clues to the underlying pathogenesis, pathologists are often not made aware of the clinical situation. Thus, it is reasonable to sign reports as multiple bilateral benign adrenal cortical nodules and give a range in size.

## 5. Summary

The classification of endocrine and neuroendocrine tumors continues to evolve with increased understanding of the underlying pathogenesis and genetic susceptibility. The high-grade follicular cell derived non anaplastic thyroid carcinoma category accounts for moderately differentiated tumors that lack the solid trabecular and insular growth pattern of poorly differentiated carcinomas, but have high-grade features and includes PTC with high-grade features. This alerts clinicians to the significance of differentiated carcinomas with high-grade features. The clonal neoplastic nature of primary multi glandular parathyroid disease resulted in change in the nomenclature and classifying these lesions as adenomas. The new category of an atypical parathyroid tumor is unique in that is a tumor extremely worrisome about parathyroid carcinoma due to the presence of atypical features but does not show definitive invasion. This is not a category for parathyroid adenomas with focal fibrosis or a few mitoses. Much has been learned about the significance of the parafibromin immunostain in parathyroid disease. In sporadic parathyroid tumors, loss of parafibromin nuclear staining is concerning for parathyroid carcinoma. But not all parathyroid carcinomas show loss of parafibromin. Hopefully, the future will bring greater understanding of parathyroid carcinomas that are not associated with *CDC73* alterations. Classification of adrenal cortical disease continues forward with new classification algorithms. Studies continue to search for a pattern of CYP11B2 immunostaining to further predict complete clinical success in primary unilateral aldosteronism. Recognizing the underlying genetic alterations in micronodular and macronodular adrenal cortical disease will continue to advance understanding of the pathogenesis of disease.

**Table 6**
Nodular adrenal cortical disease.

| Sporadic Nodular Adrenocortical Disease | Bilateral MICROnodular Adrenocortical Disease | | Bilateral MACROnodular Adrenocortical Disease |
|---|---|---|---|
| Nonfunctional<br>All ages | Endogenous Cushing syndrome<br>Children & adults <30 years | | Adults 45–60 years |
| | Primary pigmented nodular adrenocortical disease (PPNAD)<br>- Carney complex (c-PPNAD)<br>- Without Carney (i-PPNAD) | Isolated micronodular adrenocortical disease (i-MAD) | |
| Unilateral<br>Often one nodule <1 cm nodule(s) | Bilateral<br>Multiple nodules <1 cm nodules | | Multiple nodules >1 cm nodules |
| | Pigmented nodules | Non-pigmented nodules | |
| Sporadic | Germline *PRKAR1A*, or possibly *PRKACB* | Germline *PRKACA,PDE8B, PDE11A* | Germline *ARMC5* (& syndrome *MEN1, FH, APC*) |

## CRediT authorship contribution statement

**Lori A. Erickson:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Sounak Gupta:** Methodology, Writing – original draft, Writing – review & editing. **Rumeal D. Whaley:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Burak Tekin:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Jorge Torres-Mora:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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## Declaration of competing interest

Given their roles as Editor and Associate Editor, respectively, of Human Pathology, Lori Erickson and Sounak Gupta had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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