# What's new in the WHO 2022 classification of kidney tumours?

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**Summary**

The World Health Organization (WHO) 2022 classification of urinary and male genital tumours (5th edition) has significantly improved our understanding of the morphologic, immunohistochemical, and molecular characteristics of renal tumours. The aim of this review is to outline the most important changes and diagnostic updates in the WHO 2022 classification of kidney tumours. A major change in this edition is the grouping of renal tumours into broader categories that include "*clear cell renal tumours*", "*papillary renal tumours*", "*oncocytic and chromophobe renal tumours*", "*collecting duct tumours*" as well as adding two categories of "*other renal tumours*" and "*molecularly defined renal carcinomas*". Novel entities included in the WHO 2022 classification are eosinophilic solid and cystic renal cell carcinoma (ESC RCC), anaplastic lymphoma kinase (*ALK)*-rearranged RCC and *ELOC* (formerly *TCEB1*)-mutated RCC. The category of "*other renal tumours*" includes a group of diverse, unrelated renal tumours that do not fit into other categories. The group of "*molecularly defined renal carcinomas*" reflects recent discoveries in the renal tumour genomics. These molecularly-defined renal entities demonstrate a set of morphologic features reflecting genotype-phenotype relationships. Final diagnosis of such entities rests on phenotypic and immunohistochemical (IHC) correlation, usually associated with IHC surrogate makers that reflect specific genetic abnormalities.

**Key words:** kidney, renal cell carcinoma, classification, WHO, pathology

## Introduction

The new WHO 2022 classification of urinary and male genital tumours (5th edition) succeeds the previous WHO 2016 classification (4th edition) [1]. The recent advances and published evidence since the last edition have significantly improved our understanding of the morphologic, immunohistochemical, molecular, epidemiologic and clinical characteristics of various renal tumours. These advances have also been reflected in the recent updates from the Genitourinary Pathology Society (GUPS) on existing and novel/emerging renal tumours [2,3], most of which have been adopted in WHO 2022 classification.

WHO 2022 classification was prepared by 181 authors and an Editorial Board featuring standing and expert members on urinary and male genital organs, who worked together to produce the 5th edition of the WHO Blue Book on urinary and male genital tumours [4]. The final hard copy is printed in lighter blue color (to visually distinguish it from previous editions printed in darker blue) and contains more than 900 high-quality images and over 3600 references [4].

In this review, we first provide a general overview of the conceptual and organizational changes in the new WHO classification, followed by the highlights of the changes introduced in the classification of existing kid-

**Table I.** Summary of most important changes in the WHO 2022 classification of kidney tumours.

| Renal Tumour Entity | Key changes in WHO 2022 |
|---|---|
| Papillary renal cell carcinoma (PRCC) | Subclassification into type 1 and type 2 PRCC no longer recommended<br>Morphologic spectrum of PRCC expanded to include the following patterns: biphasic PRCC, papillary renal neoplasm with reverse nuclear polarity, and Warthin-like PRCC |
| Clear cell papillary renal cell tumour | Name change from "carcinoma" to "tumour" owing to benign behavior |
| *TFE3*-rearranged RCC and *TFEB*-altered RCC | Previously considered together as "MIT family of RCCs".<br>Now separated into two distinct types: *TFE3*-rearranged RCC and *TFEB*-altered RCC (that includes *TFEB*-rearranged RCC and *TFEB*-amplified RCC). |
| Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) | FH-deficient RCC is the preferred name over hereditary leiomyomatosis associated RCC |
| SMARCB1 (INI1)-deficient renal medullary carcinoma | Name change from former "medullary carcinoma" |
| Eosinophilic solid and cystic renal cell carcinoma (ESC RCC) | New entity (included under "Other renal tumours") |
| Anaplastic lymphoma kinase-rearranged renal cell carcinoma (*ALK*-rearranged RCC) | New entity (included under "Molecularly defined renal carcinomas") |
| *ELOC* (formerly *TCEB1*)-mutated RCC | New entity (included under "Molecularly defined renal carcinomas") |
| Low-grade oncocytic tumour (LOT) | Emerging entity (included under "Other oncocytic tumours of the kidney") |
| Eosinophilic vacuolated tumour (EVT) | Emerging entity (included under "Other oncocytic tumours of the kidney") |
| Oncocytic renal neoplasms of low malignant potential NOS | Suggested name for eosinophilic/oncocytic tumours with borderline features between oncocytoma and chromophobe RCC that do not fit into any specific entity. This term should be used for a group of heterogeneous sporadic, eosinophilic/oncocytic tumours with borderline features (included under "Other oncocytic tumours of the kidney").<br>"Hybrid oncocytic tumors" is a suggested term for eosinophilic/oncocytic tumours with borderline features that occur in a hereditary setting, such as Birt-Hogg- Dubé syndrome. |

ney tumour entities, and finally, we highlight several novel renal entities featured in the classification. Our aim is to outline the most important changes and diagnostic updates in the WHO 2022 classification of kidney tumours that are summarised in Table I.

## WHO 2022 classification - Organisational structure and general changes

The new 2022 WHO classification of urinary and male genital tumours (5th edition) introduced several significant changes and revisions in the classification of kidney tumours. A major organisational change is the grouping of renal tumours into broader categories that include "*clear cell renal tumours*", "*papillary renal tumours*", "*oncocytic and chromophobe renal tumours*", and "*collecting duct tumours*". In addition, two separate categories have been created, entitled "*other renal tumours*" and "*molecularly defined renal carcinomas*". The category of "*other renal tumours*" includes a group of diverse, unrelated renal tumours that do not fit into other categories. Some tumours included in this category have been previously recognised (e.g. mucinous and tubular spindle cell carcinoma, acquired cystic disease –associated renal cell carcinoma), while some are novel renal entities (e.g. eosinophilic solid

and cystic renal cell carcinoma). Another novel category of "*molecularly defined renal carcinomas*" has also been created, reflecting the recent discoveries in renal tumour genomics. However, the molecularly-defined renal entities in this category also demonstrate a set of associated morphological features or constellations of morphologies, reflecting genotype-phenotype relationships. Although such morphologies and associated IHC features may raise diagnostic suspicion for specific entities, the final diagnosis of these entities rests on the correlation of the phenotypic and IHC features, typically followed by a confirmation of their specific genetic abnormalities. Another example of a specific genetic abnormality present in a group of related renal neoplasms (considered "*metanephric tumours*"), includes BRAF p.V600E, found in most cases of metanephric adenoma, metanephric adenofibroma and metanephric stromal tumour [5,6]. The category of "*metanephric tumours*" has however remained a separate one, as in the WHO 2016 classification.

The new WHO 2022 classification has also introduced an organisational change in creating separate chapters for non-epithelial tumours common to multiple genitourinary organs (e.g. neuroendocrine, mesenchymal, hematolymphoid and melanocytic), as well as it has devoted a separate chapter dedicated to genetic tumour syndromes of the urinary and male genital tract.

As a major conceptual change, a section of "*essential and desirable diagnostic criteria*" has been introduced for each entity included in the classification, to facilitate the recognition of key morphologic diagnostic criteria, combined with the IHC and/or other relevant findings, including molecular ones.

The new WHO 2022 classification also includes a "state of understating of WHO/ISUP grade" in the context of the published literature for renal tumour types, and provides a guideline for possible use of grading for entities for which grade validation is currently lacking. The nuclear grade has been integrated into various prognostic tools for renal cancer, and its application is validated and should be used in practice for clear cell and papillary RCC (and not, for example, for chromophobe RCC). The current recommendation is that grading should be based on the highest grade represented by at least one high-power field [7]. Although such an area has not been specifically defined, it is approximately 0.23 mm$^2$ in most modern microscopes [8].

Another novelty in comparison with the previous 4th edition of WHO 2016 is introduction of ICD-O topographical coding and ICD-O morphological coding for each organ that includes a topography (T) code and morphology (M) code, respectively. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. However, behaviour code /6 is not generally used by cancer registries. TNM staging (8th edition) for urologic tumours pertaining to individual organs is also included in the current WHO 2022 edition.

## WHO 2022 classification changes in some existing renal entities

### PAPILLARY RENAL CELL CARCINOMA

Papillary renal cell carcinoma (PRCC) has been traditionally divided into 2 histologic types, type 1 and type 2. In the 5th edition of WHO 2022 classification, subtyping into type 1 and 2 is not recommended and "type 1 PRCC" is regarded as the "classic PRCC" [9]. Renal cancers previously labelled PRCC "type 2" have significant morphologic variability and a spectrum of clinical behaviors. Importantly, many tumours with prominent papillary architecture, previously considered "type 2" PRCC, have been subsequently recognised as distinct and separate entities, for example, sporadic FH-deficient RCC, MiTF family translocation RCC,

*ALK*-rearranged RCC, acquired cystic disease-associated RCC (ACD-RCC), and eosinophilic solid and cystic RCC [10]. Recent evidence from large contemporary PRCC cohorts also argues against the clinical significance ascribed to "type 1 and 2" PRCC, while supporting the prognostic value of WHO/ISUP grade and other emerging biomarkers, such as ABCC2 [11-13]. The morphologic spectrum of PRCC has also been expanded to include several distinct PRCC patterns that have been recently described, including biphasic (alveolar/squamoid) PRCC that often may have solid growth (Fig. 1A-B), papillary renal neoplasm with reverse polarity (Fig. 1C-D), previously also described as "oncocytic low-grade PRCC"; and Warthin-like PRCC that mimics salivary gland Warthin tumour (Fig. 1E) [9]. Some of these patterns have been associated with specific immunohistochemical features and molecular alterations. For example, papillary renal neoplasm with reverse polarity is consistently positive for GATA3 and is negative vimentin, and has recurrent *KRAS* mutations, even in very small tumours [14,15].

### CLEAR CELL PAPILLARY RENAL CELL TUMOUR

The name of clear cell papillary RCC has been changed to "clear cell papillary renal cell tumour" (CCPRCT) in the new WHO 2022 classification [16] as no metastatic disease or aggressive behavior have been reported since the initial descriptions of this tumour, more than a decade ago [17-19]. CCPRCT may also occur in end stage kidney disease and as multiple tumours, and their management can sometimes be challenging. Tumours with CCPRCT histology have also been reported in patients with VHL syndrome, as well as focally in otherwise typical in clear cell RCC. However, in both instances, they were more closely genomically related to clear cell RCC rather than to CCPRCT.

### TFE3-REARRANGED RENAL CELL CARCINOMA AND TFEB-ALTERED RENAL CELL CARCINOMA

In the previous WHO classification 2016 (4th edition), *TFE3*-rearranged RCC and *TFEB*-rearranged RCC have been grouped together under the joint category "MIT family of RCCs". Given the recent recognition of *TFEB* amplified RCCs, and their specific demographic predilection and clinical relevance (i.e. older patients and worse prognosis) vs *TFEB*-rearranged RCCs, both *TFEB* RCC categories have now been included as "*TFEB*-altered RCCs" in the new WHO classification 2022 [20]. The category of *TFEB*-altered RCC has also been separated from the *TFE3*-rearranged RCC [21], and the initial category of "MIT family of RCCs" has been abandoned.

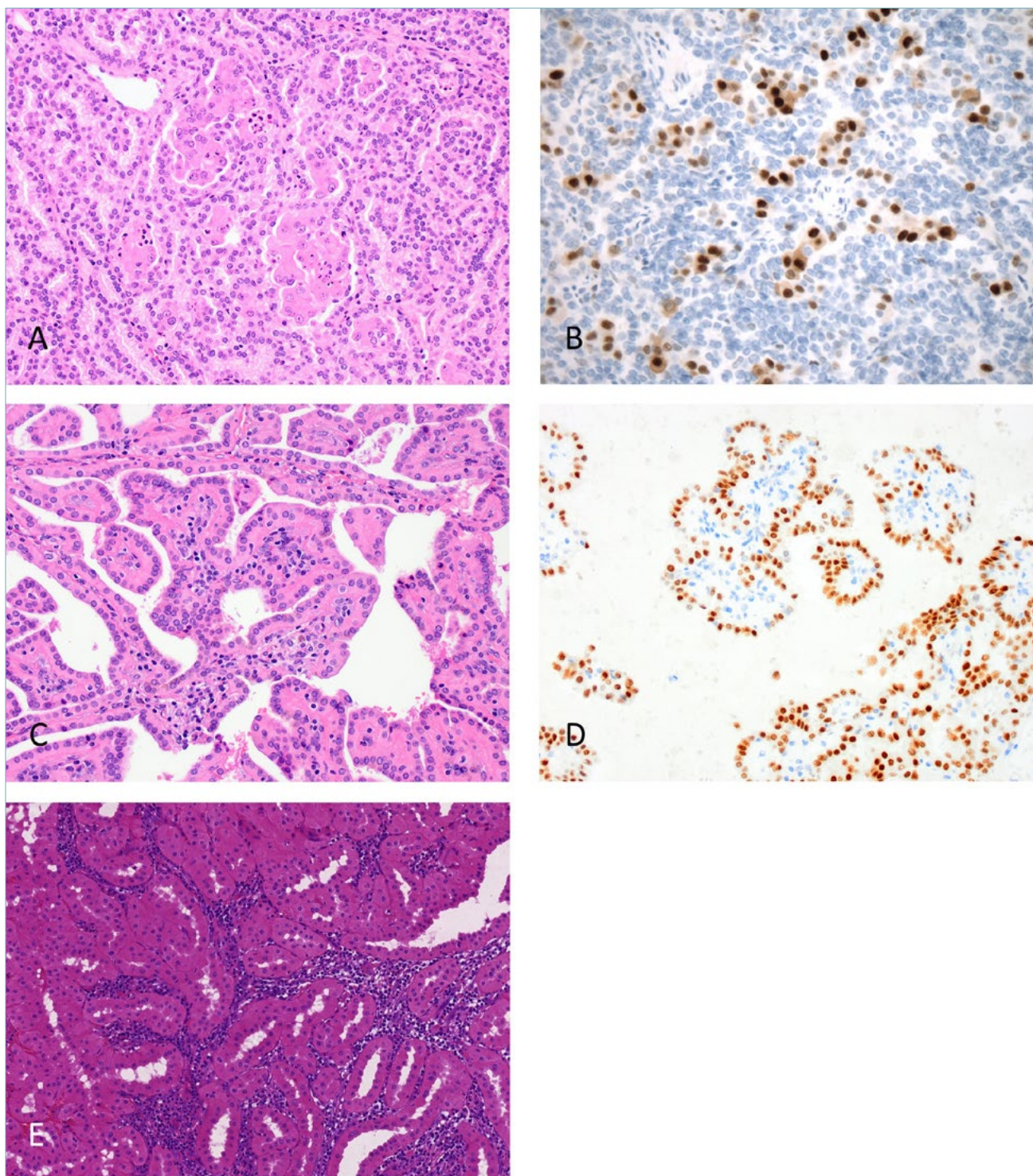*TFE3*-rearranged RCCs (also known as Xp11 trans-

**Figure 1.** Papillary renal cell carcinoma (PRCC) – novel patterns. (A) Biphasic (alveolo-squamoid) PRCC with larger eosinophilic cells showing frequent emperipolesis (cytophagocytosis), surrounded by smaller amphophilic to basophilic cells. (B) Cyclin-D1 immunoreactivity is present in the larger cells. (C) Papillary renal neoplasm with reverse nuclear polarity is consistently positive for GATA3 (D). (E) Warthin-like PRCC demonstrates brisk inflammation mimicking Warthin tumour of the salivary gland.

location RCC) are characterised by fusions of *TFE3* (Xp11) with multiple partner genes enriched in chromosomes 1, 17, and X, most commonly including *ASPSCR1*, *PRCC*, and *SFPQ* [21]. However, the list of partner genes has grown considerably in recent years (> 20), to include, for example, genes in the proximity of Xp11 that demonstrate paracentric inversions, such as *RBM10*, *GRIPAP1*, *RBMX*, and *NONO*. Such genetic variability in *TFE3*-rearranged RCCs has resulted in recognition of more diverse morphologic phenotypes for *TFE3*-rearranged RCCs than initially thought. Additionally, PEComas with *TFE3* rearrangements have also been identified, which typically lack PAX8 expression, and as such can be helpful in differentiating these tumours from the *TFE3*-rearranged RCCs.

*TFEB*-rearranged RCCs involve a t(6;11)(p21;q12) translocation resulting in a *TFEB-MALAT1* (formerly Alpha) gene fusion [20,22]. *TFEB*-translocation RCCs are mostly indolent, low-stage tumours. A characteristic biphasic pattern has been emphasised initially, consisting of large and small epithelioid cells and nodules of basement membrane material. However, other morphologic phenotypes have also been recently described, including oncocytic and papillary morphologies, and some demonstrating overlapping features with *TFE3*-associated RCCs and other RCCs (reviewed in [23,24]).

*TFEB*-amplification RCC demonstrates amplification of the 6p21, resulting in TFEB overexpression, along with frequent overexpression of the adjacent genes, for example *VEGFA* [25-27]. *TFEB*-rearranged RCCs occur in older patients and have a more aggressive behaviour, typically presenting as high stage tumours. Their morphology is not distinct and can be quite diverse. Reactivity for cathepsin K and melanocytic markers, as well as nuclear TFEB, can be helpful for screening *TFEB*-altered RCCs.

### FUMARATE HYDRATASE-DEFICIENT RENAL CELL CARCINOMA

Hereditary leiomyomatosis renal cell carcinoma (HLRCC) syndrome-associated RCC has been recognized as a separate entity in the WHO 2016 classification [28]. HLRCC is characterised by uterine and cutaneous leiomyomas (in females) and a predisposition to develop aggressive form of RCC, with an underlying autosomal dominant germline mutations in *fumarate hydratase (FH)*, found on chromosome 1q43 [29]. Subsequent studies have however found bi-allelic somatic *FH* alterations resulting in FH protein deficiency in patients who did not have a personal or family history of HLRCC. Such cases were often diagnosed as "unclassified high-grade RCCs" [30], "tubulocystic carcinomas with dedifferentiated foci" [31], "type 2 papillary

RCCs" and "collecting duct carcinomas" [32]. Therefore, the term "FH-deficient RCC" was preferred and was adopted in the WHO 2022 classification [33]. FH-deficient RCC are tumours that show compatible morphology with those seen in HLRCC syndrome, along with absence of FH reactivity by IHC (highly specific, but incompletely sensitive), reactivity for S-(2-succino)-cysteine (2SC) (highly sensitive, but incompletely specific), in a setting of uncertain clinical and family history of skin and uterine leiomyomas, and unknown genetic status [30, 31].

FH-deficient RCCs exhibit a broad morphologic spectrum that overlaps with the RCCs found in the setting of HLRCC syndrome, and both typically exhibit multiple patterns, including papillary, tubular, tubulocystic, cribriform, solid/sarcomatoid, and cystic elements (Fig. 2A-D). The most characteristic, but non-specific cytologic feature is the presence of a prominent "cherry-red" inclusion-like nucleoli, that are present at least focally [34,35].

### SMARCB1 (INI1)-DEFICIENT RENAL MEDULLARY CARCINOMA

The WHO 2022 classification introduced a change in the name of renal medullary carcinoma. These types of carcinomas show uniform loss of nuclear expression of SMARCB1 (INI1 SNF5, BAF47) protein, and therefore have been renamed as "SMARCB1-deficient renal medullary carcinomas" [36-39]. These are rare and aggressive types of carcinomas that occur almost exclusively in the renal medulla of young patients of African ancestry, who have sickle cell trait or rarely other haemoglobinopathies [40,41].

A loss of SMARCB1 protein has also been found in rare renal carcinomas that are morphology indistinguishable from renal medullary carcinoma, occccuring in patients without haemoglobinopathies (also known as "RCC, unclassified, medullary phenotype") [42-44]. The 5th edition of WHO recommnded that such tumours are regarded as a subtype of SMARCB1-deficient RMC [39]. However, SMARCB1 loss can also be found rarely in other recognisable RCC types, typically showing either dedifferentiation or rhabdoid morphology, where they likely represent a secondary event [39]. It is recommended that such tumours are classified according to their primary type (e.g. clear cell RCC with rhabdoid/dedifferentiated morphology).

## Novel and emerging renal entities in the WHO 2022 classification

### EOSINOPHILIC SOLID AND CYSTIC RENAL CELL CARCINOMA

ESC RCC is a recently described renal entity that was included as a novel entity in the WHO 2022 classi-
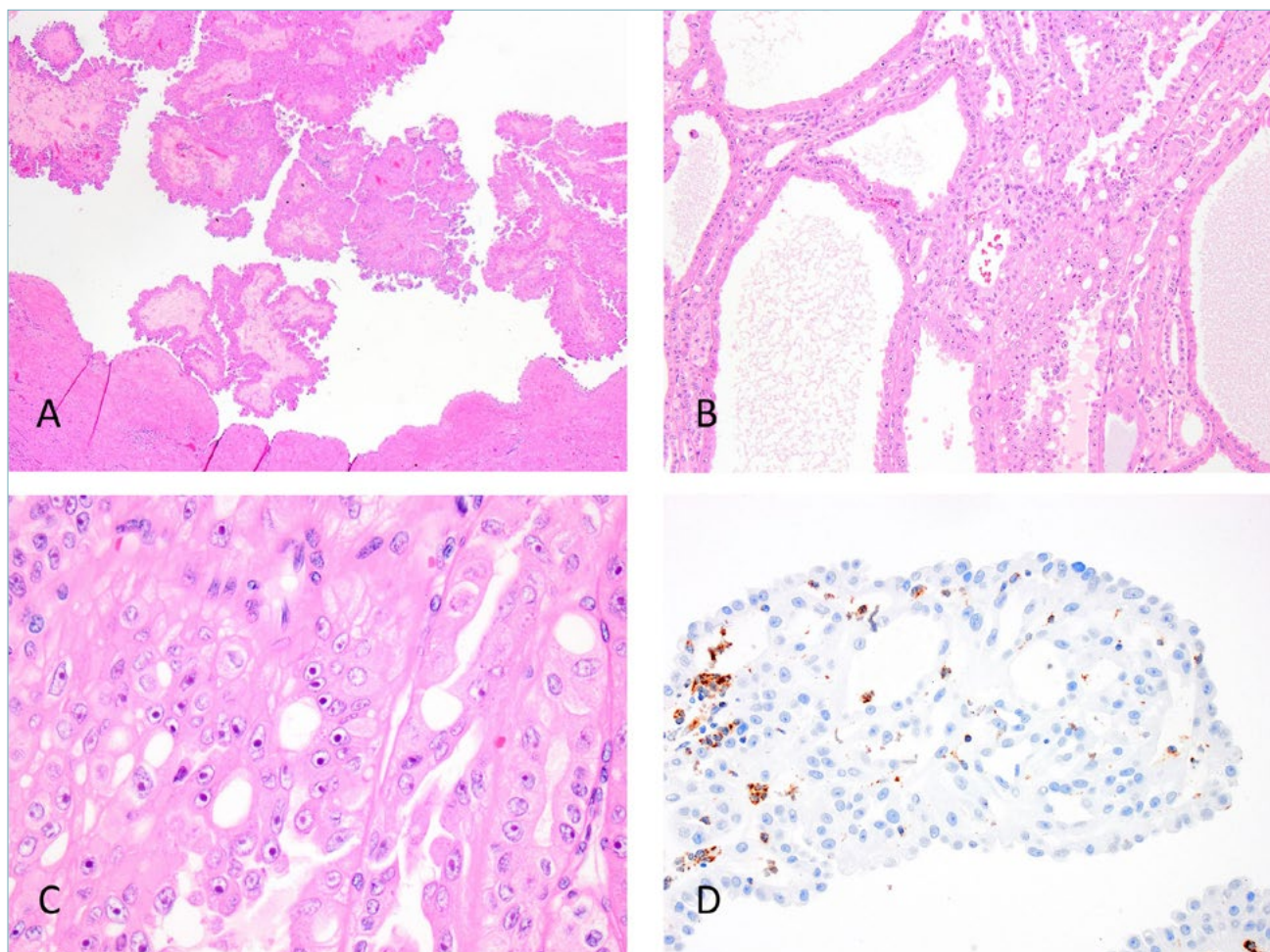
**Figure 2.** FH-deficient RCCs usually presents with a variable morphologic patterns that frequently include papillary and intracystic (A) and tubulocystic growth (B). Prominent "cherry-red" nucleoli are at least focally present (C). FH immunostaining is absent in the tumour cells (D).

fication, under the category "*other renal tumours*" [45]. ESC RCC is found mostly as a sporadic and solitary tumour in patients of broad age range, with marked female predilection [2,46-48]. Rare cases have also been identified in patients with tuberous sclerosis complex (TSC) [49,50]. Great majority of ESC RCCs had indolent behaviour, but rare tumours with metastases have also been reported, typically of larger size, and showing necrosis and haemorrhage [51-53].

ESC RCC exhibits grossly identifiable solid and cystic components in great majority of cases; only rare cases had almost exclusive solid growth with rare microcysts. The solid areas are composed of eosinophilic cells exhibiting diffuse, compact acinar or tight nested growth, and voluminous cytoplasm; other growth patterns may also be focally seen (Fig. 3A-C) [46,47]. The cells lining the cysts typically show hobnailing. A char-

acteristic feature is the presence of coarse, basophilic to purple, coarse cytoplasmic granules (stippling), corresponding to aggregates of rough endoplasmic reticulum and granular cytoplasmic material seen on electron microscopy. Scattered foamy histiocytes and lymphocytes are also common.

On IHC, ESC RCC shows either diffuse or focal CK20 expression (Fig. 3D), but rare cases may be CK20 negative; CK7 is typically negative [2,46,47]. At least focal cathepsin K expression has been reported in most cases [51]. Other positive stains include PAX8, AE1/AE3, CK8/18 and vimentin. ESC RCC is consistently negative for CD117 (KIT) and CAIX. ESC RCCs have been found to demonstrate biallelic loss in *TSC2* or *TSC1,* resulting in activation of the mTOR complex 1, but other significant genetic findings have not been identified [2,51,54,55].
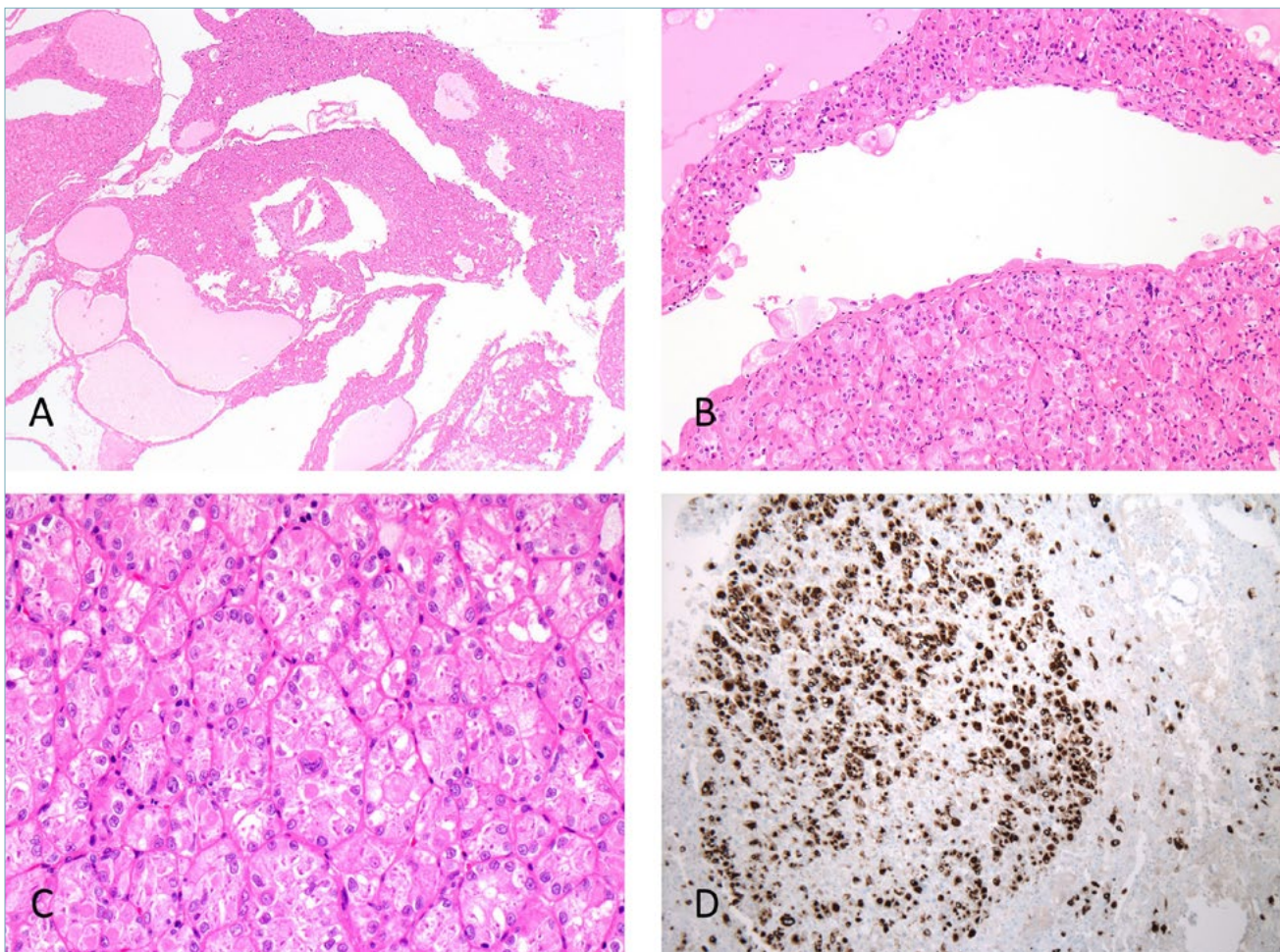
**Figure 3.** Eosinophilic solid and cystic renal cell carcinoma (ESC RCC) shows solid and cystic areas (A). The cells have eosinophilic cytoplasm and indistinct borders (B). Cytoplasmic stippling (or coarse cytoplasmic granules) is a helpful and virtually ever-present finding (C). CK20 is diffusely or focally positive (D).

## ANAPLASTIC LYMPHOMA KINASE-REARRANGED RENAL CELL CARCINOMA

*ALK*- rearranged RCC was first described in 2011 [56, 57] and was considered an emerging/provisional entity in the previous WHO 2016 classification (4th edition). In the new WHO 2022 classification it has been included as a new renal entity, within the section on molecularly defined renal carcinomas. *ALK*-rearranged RCC is characterized by an *ALK* gene fusion [58]. *ALK* is located on chromosome 2p23 and its fusion with various partner genes, such as *VCL, HOOK1, STRN, TPM3, EML4*, *PLEKHA7, CLIP1, KIF5B,* and *KIAA1217* [2,59] leads to aberrant *ALK* activation.

*ALK*- rearranged RCC has been reported in patients of a wide age range and of diverse racial backgrounds [59]. A*LK*- rearranged RCC is a clinically important diagnosis owing to the availability of ALK inhibitor targeted

therapies [60,61]. The majority A*LK*-rearranged RCCs are indolent, and aggressive clinical course and metastatic disease have been reported in a minority of cases [2,59].

*ALK*- rearranged RCC is a solitary and circumscribed tumour and typically shows heterogeneous and diverse morphology that includes various growth patterns, including papillary, solid, tubular, trabecular cystic, cribriform, signet-ring, single cells, "mucinous tubular and spindle cell RCC-like" and "metanephric adenoma-like" (Fig. 4A-F) [2,59]. A mucinous component (intracellular or interstitial) has been commonly found and this finding may raise suspicion for *ALK*-rearranged RCC in the differential. Screening for ALK by immunohistochemistry (e.g. using a monoclonal ALK antibody 5A4) (Fig. 4E) or by molecular methods (FISH or sequencing) should be performed in all dif-
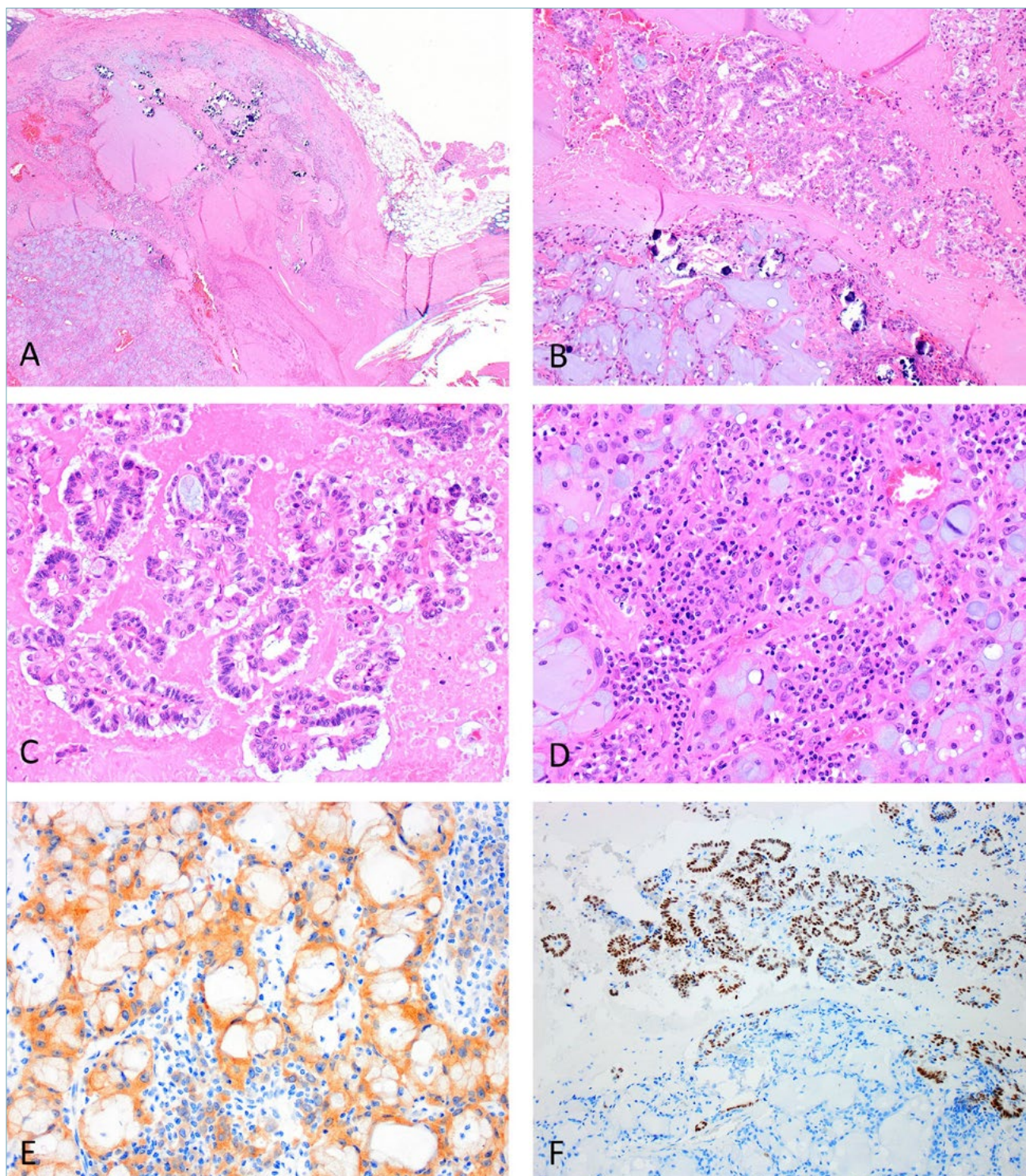
**Figure 4.** *ALK*-rearranged RCC has typically heterogeneous morphology. (A) A circumscribed tumour with peripheral pseudocapsule seen at low power, with easily recognisable pools of mucin and aggregates of psammoma bodies/calcifications. (B) At higher power, papillary formations can be seen (top), adjacent to tubules with luminal mucin (bottom). (C) Papillary formations are set in a necrotic background. (D) Foci of mucin-containing signet-ring cells with an inflammatory background were also present. (E) ALK immunostaining is positive in the neoplastic cells. (F) Papillary formations also demonstrated unusual nuclear immunoreactivity for TTF1 (thyroglobulin was negative, not shown).
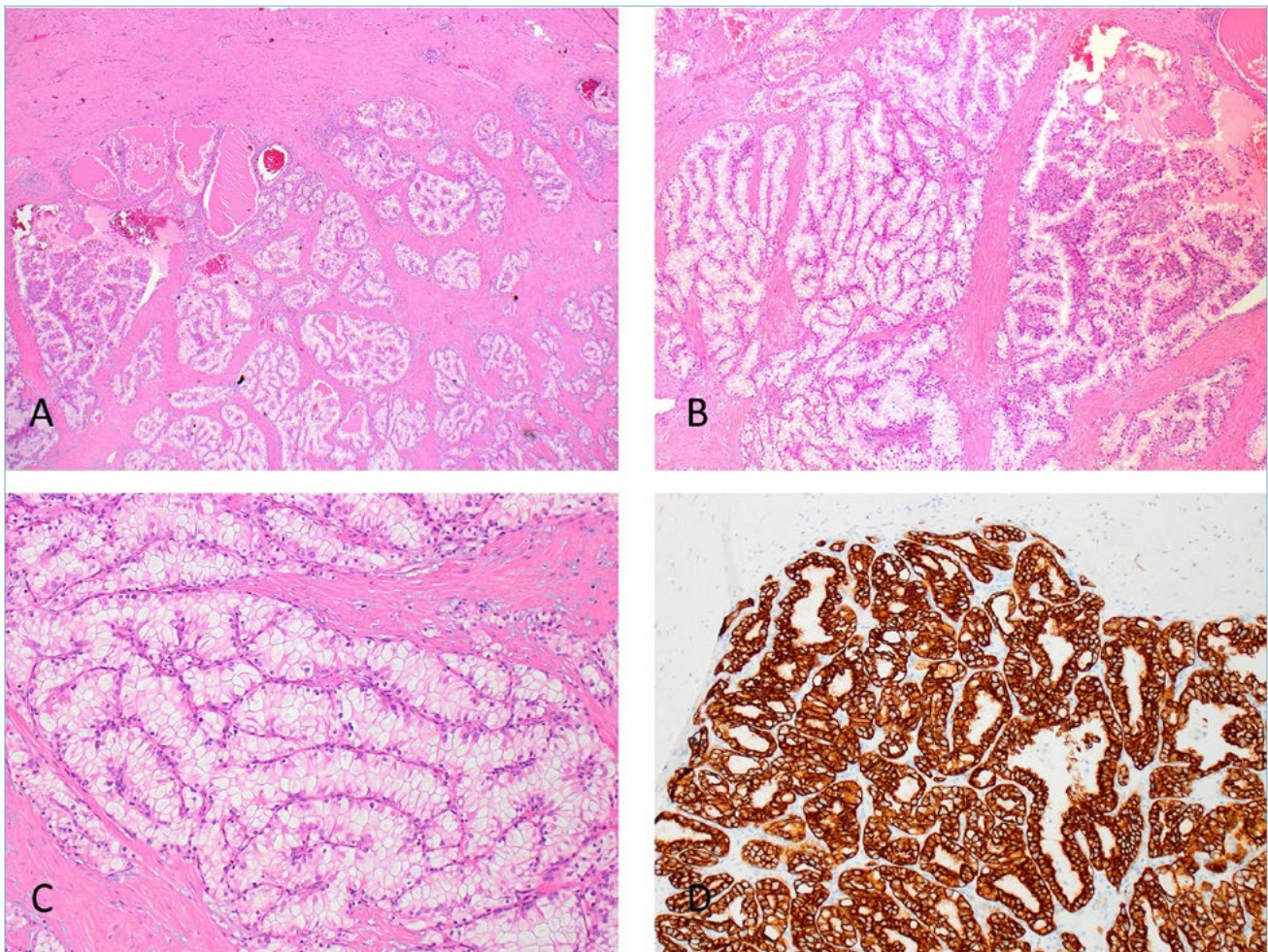
**Figure 5.** *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma. (A) Thick fibromuscular bands are present at the tumoural periphery that separate areas with clear cell morphology. (B) Clear cell areas show compact growth and focal papillary formations (seen on the right). (C) Neoplastic cells often form branching tubules with clear cells and with often voluminous cytoplasm. (D) CK 7 immunostain is diffusely positive.

ficult to classify renal tumours demonstrating variable admixed patterns, unusual morphologies, or containing a mucinous component [59].

### ELOC (FORMERLY TCEB1)-MUTATED RENAL CELL CARCINOMA

*ELOC* (formerly *TCEB1*)-mutated RCC has been included in the WHO 2022 classification as a new renal entity, under the category of "*molecularly defined renal entities*" [62]. *ELOC*-mutated RCC shows recurrent hotspot mutations of the *ELOC* (*TCEB1*) gene (8q21), encoding for elongin C, and this is considered an essential criterion to diagnose this entity. *ELOC*-mutated RCC usually demonstrates thick fibromuscular bands at the tumoural periphery that also separate areas with clear cell morphology within the tumour (Fig. 5A-D). The neoplastic cells exhibit clear and of-

ten voluminous cytoplasm and form solid acinar and focal papillary formations. However, some sporadic RCCs driven by *TSC/mTOR* mutations, referred to as "RCC with fibromyomatous or leiomyomatous stroma", and a subset of similar tumours in TSC patients, can show essentially indistinguishable morphologic features from *ELOC*-mutated RCCs [63]. In fact, similar cases have also been reported in the literature under various names, mostly prior to the molecular era (reviewed in [64]).

The previous WHO 2016 classification mentioned the "RCC with (angio)leiomyomatous stroma" as an "emerging/provisional entity" [1]. It is mentioned in the introduction section of the WHO 2022 classification [65] that "RCCs with prominent leiomyomatous stroma frequently harbour mutations in *TSC1, TSC2* and/
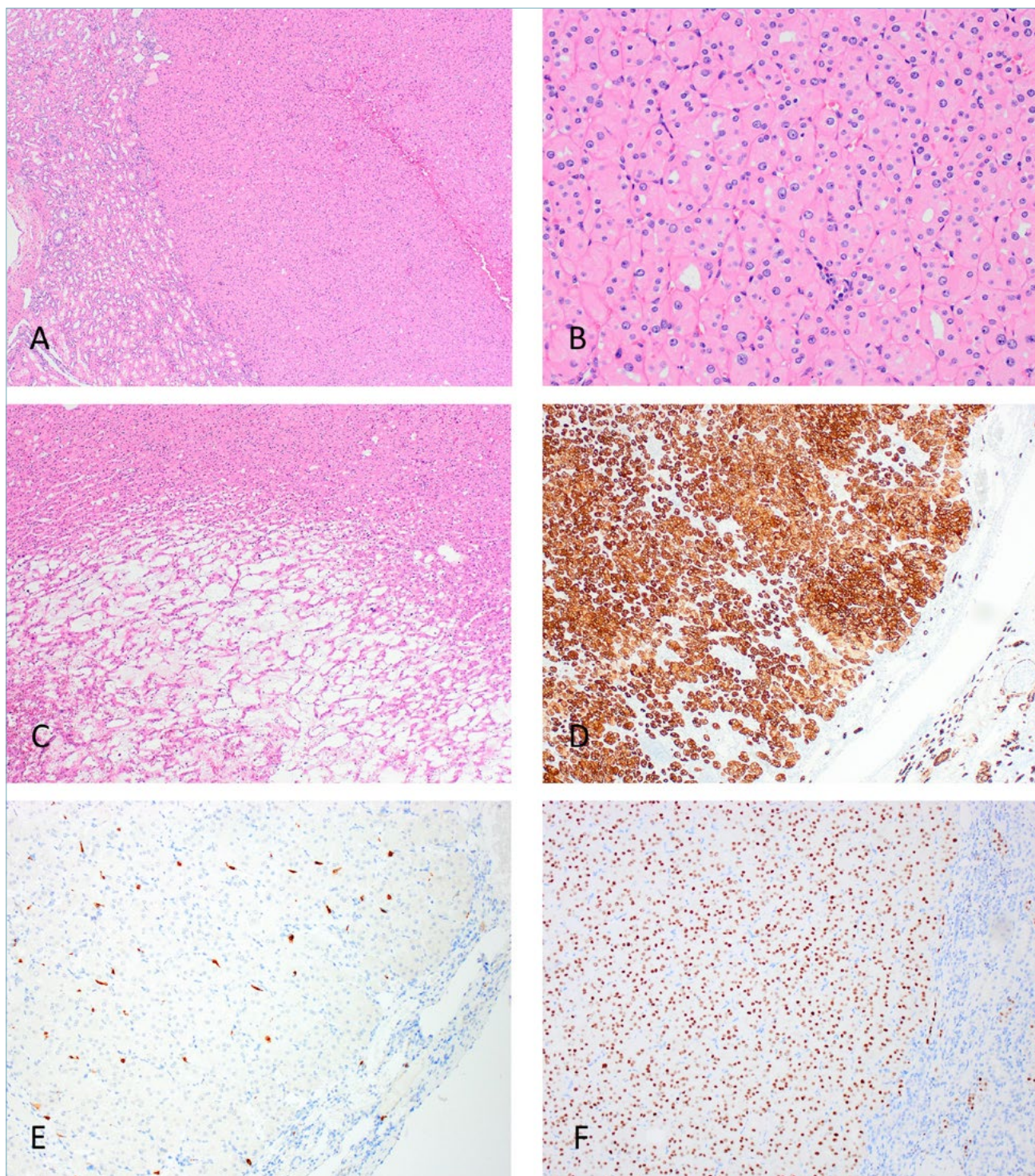
**Figure 6.** Low-grade oncocytic tumour (LOT) demonstrates solid and compact nested growth pattern without a capsule (A). Tumour cells are eosinophilic with round to oval 'low-grade' nuclei and focal perinuclear halos (B). There are focal areas of loose stroma with pauci-cellular and irregular cell composition (C). CK7 is diffusely positive (D) and CD117 is typically negative (E). GATA3 is positive in LOT (F).

or *ELOC* (*TCEB1*)", but without further elaboration or clarification. It is also stated that "a clear diagnosis of *ELOC* (*TCEB1*)-mutated RCC can only be made by complex molecular analyses" and that "without molecular corroboration, one can reasonably refer to neoplasms meeting the morphologic criteria as clear cell RCCs with prominent fibromuscular septations and CK7 positivity and give a differential diagnosis" [62,65]. To date, however, there is a limited number of fully characterised *ELOC*-mutated RCCs (< 20) and their biologic behaviour remains uncertain) [66]. They also lack a specific morphology that allows reliable distinction from other similar tumours, such as clear cell RCC and CCPRT, and their IHC profile is nonspecific, with the exception of CK7, which is typically diffuse, but can also be patchy in some cases.

The recent GUPS consensus on new and emerging entities has in fact acknowledged the dilemma whether *TSC*/*MTOR* and *ELOC*-mutated RCCs should be grouped together, based on their shared and overlapping morphology and common CK7 reactivity, despite the differing molecular alterations [2]. Based on the current evidence, GUPS supported the recognition of "RCC with fibromyomatous stroma (FMS)" as a novel subtype with morphologic, IHC, and molecular characteristics, distinct from clear cell RCC and CCPRCT. GUPS also recommended that in cases where the morphology and IHC do not provide a definitive diagnosis, to perform additional molecular evaluation for possible *VHL* gene abnormalities, as well as *ELOC* (*TCEB1*) and *TSC*/*MTOR* mutations, so that a definitive distinction between these entities can be elucidated [2]. Unfortunately, such molecular analyses are still out of reach for many pathology practices, and it is evident that more work is needed to fully characterise the spectrum of RCC FMS that also include those with *ELOC*-mutations.

## OTHER ONCOCYTIC TUMOURS OF THE KIDNEY

WHO 2022 classification has included a separate category named "*other oncocytic tumours of the kidney*", to account for a heterogeneous group of oncocytic tumours that are not classifiable either as oncocytoma or chromophobe RCC. However, in recent years, this group has been significantly reduced because of the recognition of two distinct benign oncocytic tumour entities, low-grade oncocytic tumour (LOT) [64,67] and eosinophilic vacuolated tumour (EVT) [68,69]. Both entities have been included as emerging ones in the WHO 2022 classification in the section "*other oncocytic tumours of the kidney*" [70] and are also listed in the introduction section [65].

The remaining, still unclassifiable oncocytic renal tumours represent a heterogeneous group of sporadic tumours for which the term "oncocytic renal neoplasm of low malignant potential, not further classified" was recommended by GUPS [3]. For multiple/bilateral tumours associated with Birt-Hogg-Dubé (BHD) or other hereditary syndromes, the term "hybrid oncocytic chromophobe tumours" (HOCT) has been proposed [3,71-73]. It has also been recommended that the term "hybrid" is strictly used for these types of hereditary oncocytic tumours, to avoid further confusions associated with the use of the term "hybrid" in a sporadic tumour setting [3,73].

## LOW-GRADE ONCOCYTIC TUMOUR

The initial descriptions of this entity postulated that LOT may represent a distinct entity [64,67]. LOT however shares features between renal oncocytoma and chromophobe RCC and is typically found as a single, sporadic tumour [64,67], but multiple tumours have also been found in patients with end-stage kidney disease [74], and in patients with TSC [75-77]. All reported LOT cases to date (> 200) have behaved indolently [67,68,74,76-79].

LOT is typically a smaller, solid tumour with mahogany-brown to tan cut surface. It exhibits solid and compact nested growth, as well as focal tubular, tubuloreticular, or trabecular growth [67,73,74,78]. The neoplastic cells are eosinophilic with round to oval 'low grade' nuclei that lack significant irregularities and may show perinuclear clearing (halos) (Fig. 6A-C). A characteristic morphology that is commonly found includes sharply delineated, edematous areas with scattered, irregularly arranged cells ("boats in a bay") [2,67]. These areas often contain fresh hemorrhage. Coagulative necrosis, nuclear pleomorphism, multinucleation, increased mitotic activity and other adverse features are typically absent.

LOT is diffusely positive for CK7 and is typically negative for CD117 [67], and is also positive for GATA3 (Fig. 6D-F) [80]. LOT has been shown to express at least focally p-S6 and p-4EBP1, both markers associated with mTOR pathway activation [77]. On electron microscopy, LOT exhibits abundant, closely packed cytoplasmic mitochondria, similar to oncocytoma [81,82]. Recent studies demonstrated common involvement of the mTOR pathway genes in LOT [76,77,80,83], while complete chromosomal gains or losses, as well as *CCND1* rearrangements were not found in LOT [74].

## EOSINOPHILIC VACUOLATED TUMOUR

Eosinophilic vacuolated tumour (EVT), another recently described entity, has also been included as an emerging renal entity in the WHO 2022 classification [2,68-71,81,83]. More than 50 EVTs have been documented to date and all reported cases were benign, without evidence of recurrence or metastases [2,68,81,83,84].

EVT is typically solitary and sporadic tumour, about 3-4 cm in size. It has been rarely found in patients with TSC [2,68,69,75,82,85,86]. EVT is a solid tumour that lacks a distinct cystic component and a well-formed capsule. Thick-walled vessels are almost always present at the periphery (Fig. 7A-C). The cells have an eosinophilic cytoplasm and exhibit marked intracytoplasmic vacuoles. The nuclei are round to oval, with prominent nucleoli that focally can be quite large [68,69,84].

EVT is typically positive for CD117 (KIT), CD10, and cathepsin K (in some cases focally) (Fig. 7D). CK7 is reactive only in rare, scattered cells [68,84]. The immunoprofile "CD117+ and CK7+ only in rare cells" resembles the immunoprofile typically found in oncocytoma. Complete losses or gains of multiple chromosomes have not been found, although isolated losses of chromosomes 1 and 19p have been reported [68]. *TSC/*

*MTOR* mutations leading to mTORC1 activation have consistently been documented in EVT [69,82-84]. A recent study also highlighted the existence of non-overlapping mutations in *MTOR*, *TSC2*, and *TSC1* in all evaluated cases, associated with low mutational rates [84].
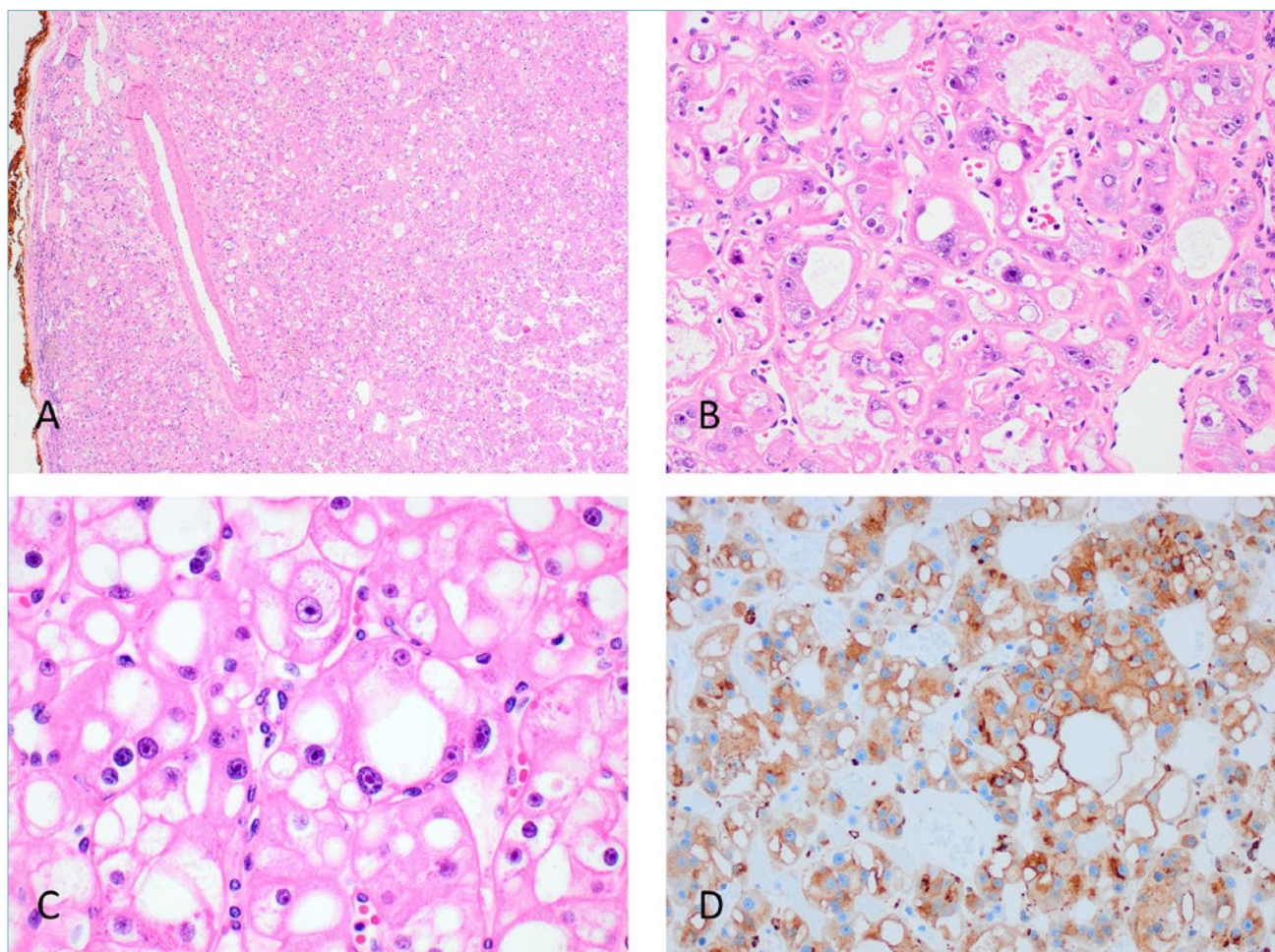
**Figure 7.** Eosinophilic vacuolated tumour (EVT). (A) EVT is a circumscribed, but unenecapsulated eosinophilic tumour, with thick-walled vessels at the periphery. (B-C) Cells show large intracytoplasmic vacuoles and round to oval nuclei with prominent nucleoli. (D) Positive immunoreactivity to cathepsin K is present.

## CONFLICT OF INTEREST

## FUNDING

## ETHICAL CONSIDERATIONS

Not applicable.

## AUTHORS' CONTRIBUTIONS

All authors contributed in the drafting and finalizing the manuscript.

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