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Report from the International Society of Urological Pathology (ISUP) Consultation Conference On Molecular Pathology Of Urogenital Cancers. III. Molecular Pathology of Kidney Cancer

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Abstract

Renal cell carcinoma (RCC) subtypes are increasingly being discerned via their molecular underpinnings. Frequently this can be correlated to histologic and immunohistochemical surrogates, such that only simple targeted molecular assays, or none at all, are needed for

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diagnostic confirmation. In clear cell RCC, *VHL* mutation and 3p loss are well known; however, other genes with emerging important roles include *SETD2, BAP1,* and *PBRM1*, among others. Papillary RCC type 2 is now known to include likely several different molecular entities, such as fumarate hydratase (FH) deficient RCC. In MIT family translocation RCC, an increasing number of gene fusions are now described. Some *TFE3* fusion partners, such as *NONO*, *GRIPAP1*, *RBMX*, and *RBM10* may show a deceptive FISH result due to the proximity of the genes on the same chromosome. FH and succinate dehydrogenase (SDH) deficient RCC have implications for patient counseling due to heritable syndromes and the aggressiveness of FH-deficient RCC. Immunohistochemistry is increasingly available and helpful for recognizing both. Emerging tumor types with strong evidence for distinct diagnostic entities include eosinophilic solid and cystic RCC and *TFEB* / *VEGFA* / 6p21 amplified RCC. Other emerging entities that are less clearly understood include *TCEB1* mutated RCC, RCC with *ALK* rearrangement, renal neoplasms with mutations of *TSC2* or *MTOR*, and RCC with fibromuscular stroma. In metastatic RCC, the role of molecular studies is not entirely defined at present, although there may be an increasing role for genomic analysis related to specific therapy pathways, such as for tyrosine kinase or MTOR inhibitors.

Keywords

renal cell carcinoma; *VHL*; molecular pathology; *TFE3*; *TFEB*; tuberous sclerosis; *MTOR*

Introduction

With increasing understanding of the genetic underpinnings of renal cancer, multiple novel subtypes of tumors have been identified (1) and our understanding of well-established renal cancer types has grown dramatically. (2) Additionally, our understanding of hereditary renal cancer syndromes has also grown to include recognition of specific tumor histologies associated with tumor syndromes. (3) Nonetheless, there remain significant practice gaps for implementation of this increasing knowledge into clinical treatment paradigms, as only a few select tumor histologies have specific treatment recommendations. (4) In 2019, in conjunction with the United States and Canadian Academy of Pathology Annual Meeting, the International Society of Urological Pathology (ISUP) convened a consensus conference on molecular pathology of genitourinary tumors. This article summarizes the recommendations of the renal cancer working group and reports the results of a survey of ISUP members with respect to molecular pathology practice in renal cancer. Since other articles have summarized in detail many of the pathologic features of renal cancer types, (5) this article focuses on the latest developments in molecular pathology of renal cancer with emphasis on aspects that are practical for the surgical pathologist.

Meeting format

A web-based survey was circulated to the ISUP membership in advance of the meeting, including a series of questions on renal cancer designed by the working group members (Table 1). Results of the survey (Supplemental File) and overviews of some key areas of emerging data in renal cancer molecular pathology were presented by the group members,

followed by a question and comment period. This article represents the consensus of the working group members and organizing committee, taking into account the survey data and open comments provided at the meeting. In contrast to some prior ISUP consensus meetings, this meeting did not include open voting by all attendees; however, any comments or concerns raised at the meeting were considered when making recommendations.

Clear cell RCC

Clear cell RCC is overwhelmingly the most common subtype of adult renal cancer, making up approximately 65–70% of tumors. (6) Much of our molecular knowledge of renal cancer stems from this type, both in the hereditary and sporadic settings. (2, 7–9) In brief, it is well known that clear cell RCC typically harbors alterations of the *VHL* gene, either in the form of mutation or promoter methylation, (2) and a “second hit” typically occurs as large deletion that may include the majority of, or the entire, p arm of chromosome 3. The latter serves as a potential diagnostic marker, as it can be detected by FISH or other copy number assessment techniques, (10) although 3p loss alone may not be entirely specific for clear cell RCC, having been identified in select other histologies. (11–13) There is emerging evidence that 3p loss and *VHL* mutation are so common in clear cell renal cancer (>90%) that some of the rare tumors lacking them may in fact be misclassified. (14) However, bringing to bear all the necessary techniques to detect these abnormalities (mutation analysis, copy number assessment, and methylation studies) are certainly beyond the scope of most diagnostic pathology practices in a routine setting.

Additionally, there is now increasing awareness of a number of other genes that are frequently altered in clear cell RCC, several of which also reside on chromosome 3p (*SETD2, BAP1, PBRM1*) (15) and several of which are involved in chromatin remodeling. Tumors with *BAP1* or *SETD2* mutations appear to have more aggressive behavior, whereas *PBRM1* mutated tumors may have more favorable behavior. (6, 15) In current practice, it appears that this information is not being used routinely, based on the low rates of survey respondents utilizing these markers and the lack of their inclusion in current clinical guidelines. (4) However, these may have emerging roles in renal cancer as our integration of molecular pathology matures.

Carbonic anhydrase IX immunohistochemistry

A relatively robust surrogate for pathology practice in supporting clear cell RCC genetics is immunohistochemistry for carbonic anhydrase IX. As part of the downstream hypoxia pathway under VHL, clear cell cancers typically show diffuse membrane staining for this marker, although staining may be decreased in aggressive or poorly-differentiated tumors. (16–21) Several caveats are necessary when using this as a surrogate for molecular pathology. First, positivity can be encountered in non-renal tumors. (18) As such, this should be used cautiously when considering site of origin for a cancer of unknown primary, especially in patients who have no apparent renal mass or history of renal cancer. Secondly, since carbonic anhydrase IX is part of the hypoxia pathway, some degree of positive staining can be encountered in any tumors or tissues with hypoxia or ischemia (Figure 1), which can be misleading in small biopsy samples with limited tissue visualization or necrosis with

scant viable cells. Finally, clear cell papillary RCC and potentially related neoplasms, discussed later, have consistent labeling for carbonic anhydrase IX despite usual absence of *VHL* alterations. A “cup-shaped” pattern of staining has been reported in particular with clear cell papillary RCC. (22)

Working Group Recommendations, Clear Cell RCC:

- In difficult diagnostic cases, molecular evaluation can be used to support a diagnosis of clear cell RCC, such as chromosome 3p loss (FISH, cytogenetics, or copy number analysis) or *VHL* mutational analysis, with the understanding that 3p loss may not be entirely specific for clear cell RCC in all contexts
- Routine use of molecular pathology is not necessary for straightforward cases of clear cell RCC
- Carbonic anhydrase IX can be used as a surrogate for molecular pathology in most cases; however, positivity can also be observed in non-renal tumors, hypoxic tissues, and clear cell papillary RCC

Papillary RCC

Papillary RCC is the second most common type of renal cell carcinoma, accounting for approximately 15%−19% of adult renal cancers. (23) It is traditionally classified into type 1 and type 2 tumors; however, there is increasing awareness that in particular type 2 tumors make up likely more than one diagnostic entity. To date, it appears that the most uniform subtype of papillary RCC based on morphologic, immunohistochemical, and molecular features is papillary RCC type 1. (24–26) Recent proposals have attempted to classify papillary RCC into multiple subtypes based on molecular genetic features and/or combined morphologic, immunohistochemical and molecular features. (25–27) As an immunohistochemical surrogate, one finding that appears consistent across papillary RCC subtypes is that staining for alpha-methylacyl-CoA racemase (AMACR) is typically diffuse and strong, with similar intensity that of normal proximal tubules. (21)

Type 1 Papillary RCC

Polysomy or trisomy of chromosomes 7 or 17 are the most common chromosomal changes in type 1 tumors. However, gains of chromosomes 3, 12, 16, and 20 (and less frequently gains of chromosomes 2, 4, 5, 6, 8, 13, and 18) have been also noted in type 1 tumors. Chromosomal losses have also been documented, most commonly of chromosomes 1, 2, 4, 5, 7, 8, 9, 10, 11, 14, 15, 16, 18, 19, 20, 21, and 22. (24) The hereditary papillary RCC syndrome, which manifests as innumerable type 1 tumors, is characterized by germline mutations of *MET*. (28–30) In sporadic papillary RCCs type 1, *MET* mutations are also present, although the frequency appears to be lower than in the hereditary setting, (25, 31, 32) contrasting to clear cell RCC, in which *VHL* alterations are typical in both hereditary and sporadic tumors. Amplifications of *MET* in some sporadic tumors have also been noted, and potential roles for therapy targeting MET has been reported in tumors with mutations or amplifications. (33–37)

Type 2 Papillary RCC

Type 2 papillary RCC is best considered a histomorphology manifested by multiple specific neoplasms rather than a single specific entity. Although gains of chromosomes 7 and 17 are have been previously noted to be relatively common in type 2 papillary RCC as well, these are in modern studies found in a smaller percentage of cases. Gains of chromosomes 12, 16 and 20 are noted for papillary RCC type 2. (24) Recent works, such as the Cancer Genome Atlas characterization of papillary RCC, have noted that type 2 tumors exhibit *CDKN2A* silencing, *SETD2* mutations, and increased expression of the NRF2–antioxidant response element pathway. (25) The CpG island methylator phenotype (CIMP) has also been noted as a subgroup of type 2 papillary RCC, highly associated with *FH* gene mutations and decreased expression of the mRNA, suggesting that this represents the emerging category of FH-deficient RCC (often associated with the hereditary leiomyomatosis and renal cell carcinoma syndrome / HLRCC), discussed later.

Oncocytic Papillary RCC / Papillary Renal Cell Neoplasm With Reverse Polarity

A third variant or subtype of papillary RCC is so-called oncocytic papillary RCC. (38–41) Until recently, this has been a poorly understood subcategory of papillary RCC composed of oncocytic cells. Since prior definitions in the literature have been variable, no definitive consensus regarding diagnosis of such tumors has been reached, and therefore this has not been adopted as an official diagnostic entity in the current classification schemes. (5, 23) Previous studies have shown a variable copy number alteration pattern with some showing gains of chromosomes 7 and 17. (39–41) Recent work has suggested that when defined according to strict criteria, there may be a distinct entity within the tumors previously noted as oncocytic papillary RCC. (26, 42, 43) In the classification scheme by Saleeb et al, this subtype was considered type 4 papillary RCC (oncocytic low-grade), (26) and recently, Al-Obaidy et al have proposed this to represent a distinct entity using the nomenclature “papillary renal cell neoplasm with reverse polarity.” (42, 43) These tumors have oncocytic cells, papillary architecture, and nuclei aligned more toward the apex of the cells. In contrast to typical papillary RCC, they show negative immunohistochemistry for vimentin, and in contrast to oncocytoma and chromophobe RCC, they are negative for KIT. (43) These tumors also appear to have consistent positivity for GATA3, contrasting to other papillary RCC subtypes. (26, 43) Very recent studies have found that this tumor is characterized by frequent *KRAS* mutations, which differs markedly from type 1 and 2 papillary RCC, suggesting that this may be an emerging diagnostic entity in future schemes. (5, 44)

Working Group Recommendations, Papillary RCC

- Type 1 papillary RCC is the most uniform subgroup, which can usually be diagnosed by morphology. Ancillary features that may be helpful in difficult cases include common gain of chromosomes 7 and 17 and positive immunohistochemistry for cytokeratin 7
- Type 2 papillary RCC is clinically and molecularly heterogeneous. This terminology may still be used at present, but should be used cautiously after consideration of mimics, especially FH-deficient RCC

- A definite role for molecular classification schemes in papillary RCC is not yet established for routine diagnostic practice and clinical treatment; however, emerging data suggest that there are more than the historical 2 subtypes
- Strong positive staining for AMACR can be used as a surrogate for papillary RCC phenotype in the appropriate context, although not completely specific

Chromophobe renal cell carcinoma

Chromophobe RCC is a generally indolent renal neoplasm with distinct morphologic features including pale cells, sometimes described as resembling plant cells, with prominent cell borders, and smaller eosinophilic cells. Neoplastic cells have accentuated cellular borders, hyperchromatic wrinkled nuclei (raisinoid nuclei), and perinuclear clearing (halos). Despite the longstanding recognition of oncocytoma and chromophobe RCC, there is evidence that this differential diagnosis remains a challenge even today, with incomplete agreement regarding diagnostic markers, use of immunohistochemistry, and need for genetic techniques. (45) Although molecular techniques are used rarely for this diagnosis, analysis of the *FLCN* (folliculin) gene can be used to support a diagnosis of Birt-Hogg-Dubé syndrome-associated “hybrid” tumors. (46, 47) Renal oncocytosis may also be a consideration for multiple oncocytic neoplasms. (48, 49) Enumeration of the chromosomes, such as by conventional cytogenetics or copy number variation pattern, can be used for routine diagnostic cases, in which multiple chromosome losses (chromosomes Y, 1, 2, 6, 10, 13, 17, 21) are most commonly identified. (50, 51) Nonetheless, other studies have also shown chromosomal gains (chromosomes 4, 7, 15, 19, and 20), losses, and even diploid status, especially in the eosinophilic variant. (52–55) Chromophobe RCC, similar to oncocytoma, has been found to have mutations in mitochondrial genes. (51, 52, 56) *TP53* mutations are relatively common in chromophobe RCC, as are alterations of *PTEN*. (52) *TERT* gene promoter rearrangements have also been found to occur in a subset of chromophobe tumors. (52)

Working Group Recommendations, Chromophobe RCC

- Chromophobe RCC can usually be diagnosed based on typical histologic features, with supportive immunohistochemistry in difficult cases
- Chromosomal copy number pattern can be used as a diagnostic adjunct in difficult cases, which often includes losses of multiple chromosomes (chromosomes Y, 1, 2, 6, 10, 13, 17, 21).
- *FLCN* gene analysis or patient genetic counseling can be undertaken for tumors with so-called “hybrid” (chromophobe-oncocytic) morphology and in suspect clinical situations, such as multiple oncocytic neoplasms

Oncocytoma

Renal oncocytoma is a tumor composed of cells with granular eosinophilic cytoplasm and round, regular nuclei, arranged in solid or alveolar architecture. Although a number of morphologic and architectural variants have been described, such as tubular, cystic, and

telangiectatic patterns (57, 58) or so-called small cell variant, (59–63) it appears that the morphology, immunohistochemistry, and genetics remain fairly consistent with a few recurring genetic findings. (64, 65) The most used immunohistochemical markers include cytokeratin 7 (showing rare cells positive, except in scar areas), KIT (CD117, showing membranous positivity, sometimes weak), and vimentin (negative, except in scar areas). (45, 66) A specific threshold for cytokeratin 7 staining remains incompletely agreed upon. (45) Three genetic patterns are usually noted: 1) loss of chromosome 1 (in whole or in part) and loss of chromosome Y, 2) rearrangements of 11q13 (mostly translocation t(5;11)(q35;q13)), chromosome 14 deletion, and 3) a normal karyotype. (67–72) These patterns have led some to propose two or three dominant subtypes of oncocytoma. (56, 72) Recently it has been recognized that the 11q13 locus, being the site of *CCND1* gene (cyclin D1), typically represents rearrangement of *CCND1* in this subset of oncocytomas. (56, 72, 73) As such, recent series have divided oncocytomas into 2–3 types or classes, separating those with *CCND1* rearrangement from those with other copy number alterations. (56, 72) Some data suggest that cyclin D1-positive oncocytomas are more often solitary, whereas there may be more multifocality in the cyclin D1-negative patients. (73) There does appear to be some correlation of immunohistochemistry for cyclin D1 with the presence of rearrangement; (73) however, evaluation of cyclin D1 has not gained substantial traction in pathology practice at present. Other oncocytoma tumors have been noted to have loss of chromosome 1, X, Y, 14, or 21. Since this is more similar to the genetic pattern expected of chromophobe RCC, it has been speculated that this group may be a precursor to eosinophilic variant chromophobe renal cell carcinoma, which can be difficult to distinguish from oncocytoma. (56) As with chromophobe RCC, mutations of mitochondrial genes have also been found in oncocytoma. (56) Again, as with chromophobe RCC, patients with multiple oncocytic neoplasms or “hybrid” tumors may be candidates for assessment of the *FLCN* gene to evaluate for Birt-Hogg-Dubé syndrome. Otherwise, multiple oncocytic tumors may indicate renal oncocytosis. (48, 49)

Working Group Recommendations, Oncocytoma

- For the most part, oncocytoma is diagnosed based on typical histologic and immunohistochemical features
- In diagnostically challenging cases, copy number or cytogenetic techniques can be used, with which oncocytoma often shows loss of chromosome 1 or Y, rearrangements of 11q13 (*CCND1*), or a normal karyotype. There is emerging evidence that *CCND1* rearranged tumors may be a distinctive subset
- *FLCN* gene analysis or patient genetic counseling can be undertaken for tumors with so-called “hybrid” (chromophobe-oncocytic) morphology and in suspect clinical situations, such as multiple oncocytic neoplasms

Clear cell papillary renal cell carcinoma

Despite being recognized only in 2006, (74) clear cell papillary RCC has now been accepted as a well-defined diagnostic entity that likely makes up as much as 4% of RCC, making it likely the 4th most common RCC subtype. (22, 75–83) Although these tumors have been

historically most often mistaken for clear cell RCC, (82) they have a characteristic histology including branched glandular structures, nuclear alignment above the basement membrane (Figure 2), and variable papillary structures protruding into cystic spaces. (5, 82) Using immunohistochemistry, they have a characteristic staining pattern with diffuse cytokeratin 7 positivity, common high molecular weight cytokeratin and GATA3 positivity, consistent carbonic anhydrase IX staining (often in a "cup-shaped" distribution with the apical cell membrane being negative), (22) and negative results for AMACR and CD10, contrasting to typical papillary RCC and clear cell RCC, respectively. (82, 84, 85) Despite the resemblance of this entity to clear cell RCC, chromosome 3p25 loss and *VHL* gene alterations are lacking in almost all tumors. A few rare cases have been reported to have such alterations, (86) the significance of which is debatable. In general, these tumors do not have a defining pattern of recurrent genetic alterations or copy number changes. (75, 87–91) Recent work has found it to be a genomically stable tumor with severe depletion of mtDNA and a distinct metabolic phenotype.(87)

Recognition of this entity is important, as it appears to have highly favorable behavior, (92) although it may be multifocal or bilateral. Previously, no definite examples of aggressive behavior have been published; however, a recent case of a metastatic lesion with a compelling morphologic, immunohistochemical, and molecular phenotype has been reported (although the primary tumor was not resected). (93) There are occasional tumors that have mixed features of clear cell and clear cell papillary RCC, which have behavior and genetics closer to those of a clear cell RCC. Thus, when encountering a case with borderline features, it is worthwhile to evaluate with immunohistochemistry. If the staining results are imperfect, such as with positive AMACR or CD10, or with less than diffuse cytokeratin 7 staining, it is likely best to classify such tumors as clear cell RCC. (94–96)

Working Group Recommendations, Clear Cell Papillary RCC

- The expected immunohistochemical pattern of clear cell papillary RCC (cytokeratin 7, high molecular weight cytokeratin, GATA3 positive; AMACR and CD10 negative) is a relatively robust surrogate for genetics and can be used to support the diagnosis
- It is not totally clear at present whether immunohistochemical confirmation is needed even in morphologically typical cases; however, 77.4% of respondents noted using do so at present (Supplemental File)
- Immunohistochemistry should be used for any tumor with borderline features of clear cell vs clear cell papillary RCC; an imperfect staining pattern should warrant classification as clear cell RCC
- In cases that remain equivocal, genetic studies may be helpful; *VHL* mutation or chromosome 3p loss should preclude diagnosis of clear cell papillary RCC

MIT family translocation-associated RCC

In the current classification of renal cell neoplasms, tumors with *TFE3*, *TFEB*, and more recently *MITF* rearrangements are now grouped under the heading of MIT family

translocation RCC. (97) Most common are *TFE3* rearrangements, located at Xp11.2, which has led to the designation Xp11 translocation RCC for this tumor. Other works have described the recurring histologic patterns in translocation RCC tumors. (97) Common recurring features of translocation tumors include a mixture of clear and eosinophilic cells, a mixture of papillary and nested architecture, psammoma bodies, and hyalinized stroma. (98) Currently described fusion partners of *TFE3* include *ASPSCR1*, *PRCC*, *NONO*, *SFPQ*, *CLTC*, *PARP14*, *LUC7L3*, *KHSRP*, *DVL2*, *MED15*, *NEAT1*, *RBM10*, *KAT6A*, *GRIPAP1,* as well as some unknown genes. (97–105) Tumors with *ASPSCR1-TFE3* fusion tend to have more papillary architecture and psammoma bodies, whereas those with *PRCC-TFE3* fusion tend to have less abundant cytoplasm, more compact architecture, and fewer psammoma bodies. (98, 102)

Much less common than *TFE3* rearrangement is *TFEB* rearrangement in renal cancer, also known as t(6;11) RCC for the recurring translocation that fuses *MALAT1* and *TFEB.* More recently a few alternative partners have been recognized, including *COL21A1*, *CADM2*, and *KHDRBS2*. (25, 106) The prototypical *TFEB* rearrangement tumor has a unique histologic pattern of nested structures formed by cells with clear cytoplasm surrounding smaller cells with less cytoplasm and associated hyaline globules, yielding a rosette-like formation. (107) However, this is not a requirement nor entirely specific for the diagnosis, as it is sometimes not well visualized, and a similar finding can occasionally be seen in *TFE3* rearrangement tumors. (98) Tumors with TFEB amplification have been recently recognized, discussed later under emerging RCC types. (11, 108–111)

Although for many years *TFE3* and *TFEB* were considered the only members of the MITF gene family that participated in rearrangements in RCC, recent work suggests that the *MITF* gene itself can be rearranged, with one study reporting an *ACTG1-MITF* fusion (112) and another finding *PRCC-MITF*. (113) The detailed pathologic characterization of the tumor with *PRCC-MITF* fusion by Xia et al noted similar findings to translocation RCC in general, including rosette-like architecture, psammoma bodies, with positive cathepsin K but negative TFE3, TFEB, and melanocytic marker staining. (113)

Surrogates available to the pathologist to recognize translocation RCC prior to, or in lieu of, genetic studies include several immunohistochemical markers (Table 2). In contrast to clear cell RCC, translocation tumors show negative or minimal carbonic anhydrase IX staining, and often some degree of melanocytic marker positivity is present. (114) Immunohistochemical staining for TFE3 and TFEB proteins is also of value, although this can be technically difficult and dependent on the laboratory staining conditions. (98) Classically translocation carcinomas show less cytokeratin staining than RCC in general; however, again this is not an unbreakable rule, as cytokeratin positivity can also be observed. (114) Staining for cathepsin K is also useful in recognizing translocation tumors, although positivity varies depending on the specific gene fusion. (115, 116) Therefore, a positive result is highly supportive of translocation RCC, but a negative result does not exclude it. FISH studies are a mainstay of diagnosis. (117–119) However, recent work has found that several specific fusions may show a false-negative or subtle positive FISH result, due to fusion of genes located close to each other on the X chromosome, in particular *NONO*

(Figure 3), *GRIPAP1*, *RBMX*, and *RBM10*. (120–125) Therefore, other molecular studies, such as RNA sequencing or other techniques may be necessary to confirm difficult cases.

Working Group Recommendations, Translocation RCC:

- Translocation RCC should be considered when encountering RCC with a mixture of clear cell and papillary features, psammoma bodies, abnormally voluminous cytoplasm, or hyalinized stroma, or in a patient of unexpectedly young age
- Helpful pathologic surrogates for the diagnosis include positive immunohistochemical staining for TFE3 or TFEB proteins, melanocytic markers, or cathepsin K, with negative or minimal staining for carbonic anhydrase IX
- FISH for *TFE3* or *TFEB* rearrangement is a helpful diagnostic tool; however, recent work has shown that some fusions resulting from X chromosome inversion (particularly *RBM10, RBMX, GRIPAP1,* and *NONO* fusions) may show a false-negative FISH result due to the proximity of the genes involved in the rearrangement, in which case sequencing studies may be used to verify rearrangement

Renal medullary carcinoma

Renal medullary carcinoma is an aggressive renal adenocarcinoma classically found in the setting of sickle cell trait or rarely with other hemoglobinopathies. These tumors can show an infiltrative glandular architecture, often with necrosis and inflammation. (126) Recent studies have shown that medullary carcinoma is characterized by loss of the *SMARCB1* (INI1) gene, with mechanisms including hemizygous loss and balanced translocation of the gene, homozygous loss, or pathogenic somatic mutation. (127–129) As such, immunohistochemistry for the SMARCB1 (INI1) protein has emerged as a helpful diagnostic tool for this entity, showing abnormal negative staining of the tumor cells. (126, 130–132) Of note, OCT3/4, often used in diagnosis of germ cell tumors, also may show positivity in medullary carcinoma. (133) Interestingly, rare tumors have also recently been recognized to have alterations of *SMARCB1* or abnormal negative staining for the protein in the absence of sickle trait. The term “RCC unclassified with medullary phenotype” has been proposed for this scenario, until it becomes better understood. (134, 135)

Working Group Recommendations, Renal Medullary Carcinoma:

- When encountering an aggressive renal carcinoma with tubular, papillary, or infiltrative architecture, correlation with clinical history for sickle trait or other hemoglobinopathy and evaluation of SMARCB1 protein staining can be used to support a diagnosis of medullary carcinoma
- Rare carcinomas resembling medullary carcinoma with SMARCB1 loss in the absence of sickle trait or other hemoglobinopathies are currently recommended to be classified as RCC unclassified with medullary phenotype, pending further study of this rare phenomenon

Collecting duct carcinoma

Once considered one of the major subtypes of renal cancer, collecting duct carcinoma is now considered quite rare and essentially a diagnosis of exclusion after other subtypes are argued against, particularly FH-deficient renal cancer, urothelial carcinoma, metastatic carcinoma from another organ, and renal medullary carcinoma. A recent study proposed an algorithm from discrimination between these entities, all of which can be composed of infiltrative glands, papillary structures, and cribriform structures, among other patterns. (126) Such a histology, in combination with sickle trait and abnormal negative SMARCB1 staining would be diagnostic of medullary carcinoma, whereas abnormal negative staining for FH, positive staining for 2-succino-cysteine (2SC), or *FH* mutation would support FH-deficient RCC. Careful exclusion of urothelial carcinoma invading the kidney or metastatic carcinoma from another origin is also necessary before arriving at such a diagnosis. Nonetheless, there do remain a subset of tumors that would fall into the category of collecting duct carcinoma using such a system. Recent molecular characterization of collecting duct carcinoma has found most common genomic alterations in *NF2*, *SETD2*, and *CDKN2A*. A subset of tumors was noted to have alterations of *SMARCB1* or *FH* homozygous loss, (136) suggesting that these likely represent either medullary carcinoma or RCC unclassified with medullary phenotype, or FH-deficient renal cancer, respectively.

Working Group Recommendations, Collecting Duct Carcinoma:

- Collecting duct carcinoma is a diagnosis of exclusion for a tumor that has been proven to be of primary renal cell lineage (not urothelial or metastatic) and for which FH-deficient and medullary carcinoma have been argued against

Other RCC types (mucinous tubular and spindle cell carcinoma, tubulocystic carcinoma, and acquired cystic kidney disease RCC)

Mucinous tubular and spindle cell carcinoma, tubulocystic carcinoma, and acquired cystic kidney disease RCC all demonstrate some overlapping features of papillary RCC, yet each are considered currently distinct diagnostic entities, based on some unique pathologic features. (5, 137–143) Although the spindle-shaped cell areas of mucinous tubular and spindle cell carcinoma could be confused with sarcomatoid changes, these tumors are usually nonaggressive, although rare metastatic examples have been reported. (144–146) In pure form, mucinous tubular and spindle cell carcinoma has a recurring copy number variation pattern with multiple chromosomal losses involving chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22, without the gains of chromosomes 7 and 17 that is typical of papillary RCC. (147–150) Recent molecular characterization has found that this tumor also demonstrates inactivation of Hippo pathway tumor suppressor genes, with *PTPN14* and *NF2* being most common alterations. (151, 152) Recently, VSTM2A overexpression with RNA in situ hybridization has been noted as a sensitive and specific biomarker for this tumor. (153) There remains some debate as to whether tubulocystic RCC is closely related to papillary RCC, as some studies have found similar chromosomal copy number patterns (gain of chromosome 7 or 17 and loss of Y) or clustering with papillary RCC, whereas others have found trisomy 7 and 17 to be lacking in pure tubulocystic carcinoma. (140, 141, 154) Loss

of chromosome 9 has also been noted. (155, 156) It has recently been shown that some tumors that resemble tubulocystic carcinoma yet which have an abrupt transition to high-grade infiltrative carcinoma (157) are likely best classified as fumarate hydratase (FH)-deficient RCC, discussed additionally later. (158) In a genomic profiling study of tumors in end-stage renal disease, acquired cystic kidney disease RCC tumors were found to cluster more closely with papillary and clear cell papillary RCC than clear cell RCC. (89) Although gains of chromosomes 7 and 17 can be observed, resembling type 1 papillary RCC, these tumors can also show gain of chromosomes 3, 16, and Y. (142, 159–163)

Working Group Recommendations, Other RCC types

- Diagnosis of these RCC types can usually be made based predominantly on morphology
- Copy number assessment can be used in difficult cases to support diagnosis of mucinous tubular and spindle cell carcinoma, which typically shows losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22, and lack of gains of chromosomes 7 and 17
- Heterogeneity of patterns in a tumor resembling tubulocystic carcinoma should prompt consideration of FH-deficient carcinoma or hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

Hereditary renal cancer syndromes

von Hippel-Lindau disease

von Hippel-Lindau disease is the prototypical hereditary renal cancer syndrome, associated with multiple clear cell RCC tumors, renal cysts (Figure 4), and extrarenal manifestations including: hemangioblastoma of the central nervous system and retina, pheochromocytoma, pancreatic cysts and neuroendocrine tumors, epididymal and broad ligament cystadenomas, and endolymphatic sac tumors of the inner ear. (164, 165) Patients with von Hippel-Lindau disease have a germline mutation of the *VHL* gene, which is also commonly mutated in sporadic renal cancer. Therefore, only one genetic “hit” is needed for tumor development, in contrast to the typical “two-hit” mechanism expected in the sporadic setting. (3, 165, 166) The findings of the renal cancers in these disease patients generally resemble those in the sporadic setting, except that tumors and cysts can sometimes be numerous and occasionally microscopic incipient tumors can be found in the grossly normal-appearing renal parenchyma. When encountering clear cell RCC in a patient of young age (under age 46) (167) or with this constellation of multiple tumors, it would be appropriate for the pathologist to communicate with clinicians that a hereditary syndrome may be a consideration and that genetic counseling could be considered.

Of note, the renal cancers in patients with von Hippel-Lindau disease sometimes morphologically closely resemble clear cell papillary RCC, (96) which is counterintuitive since sporadic clear cell papillary RCC tumors rarely if ever harbor alterations of *VHL*. However, when using immunohistochemistry, these clear cell papillary-like tumors in von Hippel-Lindau patients typically show an atypical staining pattern, such as with incomplete

or negative cytokeratin 7 staining and positive CD10 or AMACR reactivity. Most have loss of chromosome 3p using FISH, suggesting that these are best classified instead as clear cell RCC. (96)

Working Group Recommendations, von Hippel-Lindau Disease

- When encountering a clear cell RCC in a patient under age 46 or multiple clear RCC tumors, cysts, or microscopic clear cell tumors, it is worthwhile to communicate with clinicians that evaluation for a hereditary renal cancer syndrome may be considered
- Tumors that resemble clear cell papillary RCC in von Hippel-Lindau disease patients typically do not show the expected staining pattern and are likely better classified as clear cell RCC due to the known risks of multiple renal cancers in these patients

Succinate dehydrogenase (SDH) deficient neoplasia

Autosomal dominant germline mutations of *SDHA, SDHB, SDHC* and *SDHD* cause a hereditary cancer syndrome characterized by paraganglioma/pheochromocytoma, gastrointestinal stromal tumor (GIST), RCC, and pituitary adenoma. (168, 169) Immunohistochemistry for SDHB is abnormally negative (which defines a tumor as being SDH deficient) whenever there is bialleic inactivation of any of the SDH genes. (168, 169) SDH deficiency is almost always associated with germline SDH mutations. (168–171) Care must be taken when interpreting SDHB immunohistochemistry to ensure that there are internal positive controls of non-neoplastic cells demonstrating strong granular cytoplasmic (mitochondrial) staining and to distinguish cases where the neoplastic cells show weak and diffuse staining (which is considered negative) from true positive (granular) staining (Figure 5A).

When there is double hit inactivation of *SDHA*, SDHA immunohistochemistry is also negative. (172, 173) *SDHA* germline mutations can occur in the general healthy population (up to 0.3% in some studies) (173) with a very low penetrance (currently estimated at 1.7%). (174) Therefore, the significance of *SDHA* mutations, particularly when discovered incidentally as part of a personalized medicine approach, should always be interpreted in the clinical context.

Succinate dehydrogenase deficient renal carcinoma is considered a distinct type of renal carcinoma under the WHO 2016 classification. (175) The majority of SDH deficient renal cancers demonstrate distinctive morphology illustrated in Figure 5B. (175–180) Briefly, the tumors are relatively circumscribed but entrap tubules and commonly show cystic change. The neoplastic cells demonstrate flocculent eosinophilic cytoplasm. Commonly there are distinctive, intracytoplasmic inclusions containing eosinophilic or wispy pale material, which appear to correspond to altered mitochondria. However, with the more widespread availability of screening immunohistochemistry, variant morphologies are being increasingly recognized.

Although metastasis is rare in low grade tumors, SDH deficient renal carcinomas with sarcomatoid change or coagulative necrosis are considered high risk with a metastatic rate approaching 70%. (175, 179, 180) The overwhelming majority of SDH deficient renal carcinomas reported to date have been associated with germline mutation in one of the SDH genes – usually *SDHB* or *SDHC*. Cases associated with *SDHA* mutation more commonly show variant morphology and are often identified only after molecular testing, where SDHA immunohistochemistry is particularly useful to distinguish between an incidental finding and true pathogenicity. (181–183)

Working Group Recommendations, SDH Deficient RCC

- Care is required in interpreting SDHB IHC, particularly to ensure internal positive controls are present and to identify distinguish weak diffuse (considered negative) staining.
- The diagnosis of SDH deficient RCC should be strongly considered with the stereotypical eosinophilic vacuolated cell morphology; however, variant morphologies are increasingly being recognized, such that the diagnosis may also be considered for other unusual patterns of RCC
- The overwhelming majority of SDH deficient renal cell carcinomas are associated with germline mutation of the SDH subunits (usually *SDHB*), and therefore clinical genetic counseling should typically be undertaken when this diagnosis is made

Fumarate hydratase (FH) mutation and hereditary leiomyomatosis and renal cell carcinoma (HLRCC)

Autosomal dominant germline *FH* mutation causes the HLRCC syndrome, characterized by benign leiomyomas of the skin and uterus, RCC and, rarely, pheochromocytoma. (184, 185) Similarly to SDH deficiency, fumarate hydratase deficiency can be identified by abnormal negative immunohistochemical staining for fumarate hydratase (loss). However, in contrast to SDHB, FH loss is not completely sensitive for FH deficiency and it is currently estimated that only approximately 80 to 90% of FH deficient tumors will show negative staining using immunohistochemistry. (126, 158, 184, 186–191) Positive staining for 2SC is a promising more sensitive marker of fumarate hydratase deficiency; however, limited availability has significantly limited its use and validation. (184, 186, 188) The cutaneous and uterine leiomyomas associated with FH deficiency are characterized by greater cytological atypia which commonly has a symplastic quality. (184) Other clues to the diagnosis of fumarate hydratase deficiency, best seen in uterine leiomyomas, include a staghorn vasculature and prominent nucleoli. (184, 192)

Initially the renal carcinomas arising in the setting of HLRCC were characterized as type 2 papillary RCC with prominent inclusion-like nucleoli. (193) Since then several studies have reported that morphologies are more variable and are commonly mixed. (126, 158, 186–188, 190, 191, 194) In addition to the classic type 2 papillary RCC-like appearance, other morphologies including solid, cribriform/sieve-like, tubular, cystic, low grade oncocytic, and sarcomatoid are increasingly being recognized. (188) Given this morphological variability, a

low threshold for FH and 2SC immunohistochemistry is indicated for any tumor, particularly in younger patients, that does not neatly fit into other diagnostic categories (Figure 6). Furthermore, given the limited sensitivity of FH immunohistochemistry and the relative lack of availability of 2SC, in cases with suggestive morphology it is still reasonable to proceed to molecular testing even if FH immunohistochemistry is positive.

Working Group Recommendations, FH Deficient RCC (HLRCC)

- Type 2 papillary RCC-like morphology with prominent nucleoli is helpful to recognize FH-deficient RCC and prompt confirmatory testing
- Variant morphologies with heterogeneous patterns (papillary, tubulocystic, infiltrative, or mixed architecture, with or without prominent nucleoli) are increasingly recognized and should also prompt immunohistochemistry or molecular testing
- FH negative immunohistochemistry occurs in only 80–90% of FH deficient neoplasms, therefore normal positive staining or equivocal weak positive staining does not exclude *FH* mutation; molecular testing may be considered
- Although somatic only mutations do occur (especially in uterine leiomyomas in older women), most FH deficient RCCs reported to date have been associated with germline *FH* mutation (HLRCC syndrome) and should prompt genetic counseling

Other hereditary kidney tumor syndromes

Other hereditary syndromes associated with renal tumors include the hereditary papillary RCC syndrome, characterized by mutation of *MET* and numerous papillary RCC tumors, and Birt-Hogg-Dubé syndrome, characterized by mutation of *FLCN* and multiple oncocytic neoplasms (oncocytoma and chromophobe RCC or “hybrid” tumors). (195) In addition to the well-known development of angiomyolipomas in patients with tuberous sclerosis complex, these patients can also develop RCC, including some novel subtypes such as eosinophilic solid and cystic RCC, discussed later. (196, 197) In general, there is increasing recognition of the roles of the tuberous sclerosis genes (*TSC1* and *TSC2*) in emerging subtypes of renal cancer, (198–203) discussed in the next section.

Emerging renal cancer types

Eosinophilic solid and cystic RCC

Eosinophilic solid and cystic RCC was first recognized as an unusual pattern of RCC in patients with tuberous sclerosis. (196, 197) These tumors are notable for solid and cystic growth, both composed of cells with voluminous cytoplasm and basophilic stippling of the cytoplasm (Figure 7). (203) Following the recognition of this tumor in the setting of tuberous sclerosis, it was shown that it can occur sporadically, predominantly in women, and that the tumors often have positive immunohistochemistry for cytokeratin 20 (ranging from focal to diffuse, with rare tumors negative). (203) Later it was found by several groups simultaneously that even the sporadic tumors have molecular alterations of *TSC1* or *TSC2.*

(199–201) Although initial reports suggested that these neoplasms are non-aggressive, a few recent studies have reported metastases, supporting their classification as carcinomas. (204, 205) The recurring constellation of pathologic features and molecular pathology strongly support this tumor as a novel diagnostic entity.

RCC with TSC / MTOR gene mutations

In addition to eosinophilic solid and cystic RCC, a few other subtypes of renal cancer are now being recognized to have mutations of *TSC1*, *TSC2*, or *MTOR*, again likely corresponding to some of the unique histologic patterns that were recognized in patients with tuberous sclerosis complex. (196, 197) For example, one pattern resembled so-called renal angiomyoadenomatous tumor or RCC with smooth muscle or angioleiomyoma-like stroma, (196, 206) in which there are clear cells forming glandular structures dispersed in muscular stroma or within the cores of papillary structures. (206) A subset of tumors with such morphology has been recently found to harbor mutations in *TSC1*, *TSC2*, or *MTOR.* (207, 208) Since only some of these patients have clinical stigmata of tuberous sclerosis complex, (207–210) it seems that this tumor may again have both sporadic and inherited forms associated with alterations of *TSC1, TSC2*, or *MTOR.*

Secondly, it has been recently found that some oncocytic neoplasms with vacuolated cytoplasm have *TSC2* or *MTOR* mutations, (198) which appears to correspond to an entity described by another group as high-grade oncocytic tumor. (211, 212) The clinical behavior described for these tumors thus far appears indolent. In general, these tumors exhibit a chromophobe-like histology with prominent nucleoli and eosinophilic cytoplasm with areas of cytoplasmic clearing or vacuoles. (198, 211) Some of these tumors may show histologic features overlapping with eosinophilic solid and cystic RCC (e.g. basophilic stippling of eosinophilic cytoplasm, nested or solid architecture), which may reflect their shared molecular alterations in *TSC1* or *TSC2.* Taken together, these appear to be emerging subcategories of renal neoplasms with alterations in the MTOR pathway.

TCEB1 mutated renal cell carcinoma

Although some of the renal cancers with fibromuscular stroma appear to be associated with *TSC1* or *TSC2* mutations, recent work has recognized tumors that resemble clear cell RCC with fibromuscular stroma that harbor mutations of *TCEB1* rather than *VHL*, likely accompanied by loss of chromosome 8 (often in the form of monosomy). (14, 206, 207, 213–216) It is not entirely clear at present if these tumors can be readily discriminated from clear cell RCC prospectively, as they are also positive for carbonic anhydrase IX. However, cytokeratin 7 positivity appears to be increased in this tumor type. Although initial data on this subset suggested that they are non-aggressive, recent reports of aggressive behavior have been published. (213, 217)

RCC with TFEB / 6p21 / VEGFA amplification

Although RCC with *TFEB* rearrangement has been recognized for many years, very recent work has found that occasional renal tumors exhibit amplification of chromosome 6p21 including the *TFEB* and *VEGFA* genes. (11, 108–112, 218, 219) These tumors thus far appear to be highly aggressive, with a mixture of histologic patterns predominantly

resembling papillary RCC (Figure 8), although sometimes with areas suggesting clear cell or chromophobe RCC. Like translocation RCC, these tumors have been found to have some positivity for melanocytic immunohistochemical markers, particularly melan-A (more often than HMB45), and cathepsin K is often positive. (11, 218) If break-apart FISH for *TFEB* is used, it typically reveals numerous copies of the probes (at least 10), although low-level amplification has been reported in some cases, the significance of which is less clear. (109) Most of these tumors have shown amplification in the absence of rearrangement of *TFEB*; however, both rearrangement and amplification has been reported. (111) Recent work shows that *TFEB* gene expression is increased in these tumors, although not as much as in *TFEB* translocation tumors, raising the possibility that other genes at the 6p21 locus, such as *VEGFA* or *CCND3* or other genes, may be responsible for the aggressive behavior. (108) The independent confirmation of this phenomenon by multiple groups strongly supports consideration of this tumor type as a significant diagnostic entity.

ALK rearranged RCC

Rearrangement of *ALK* has been described in various tumors. However, an increasing number of renal cancers with *ALK* rearrangement have been recently reported. (164, 220–236) *ALK* rearranged renal cancers have been reported to be mostly papillary or cribriform, some having mucin production (Figure 9) or myxoid changes. Cases with the *VCL-ALK* fusion have been associated with sickle trait and have demonstrated prominent cytoplasmic vacuolization. Several fusion partners have been identified in *ALK* rearranged RCC, including *TPM3, STRN, VCL, HOOK1*. Novel partners *CLIP1* and *KIF5B* have been identified recently. Tumors with unusual morphology have been recently noted, including resembling metanephric adenoma or mucinous tubular and spindle cell carcinoma. (228, 237) Of note, clinical response to ALK inhibitor alectinib has been reported in patients with *ALK*-rearranged tumors, implying that this may be a targetable therapeutic option. (233) For detection of *ALK* rearranged renal cancer, immunohistochemical screening with ALK antibody and confirmation by FISH or sequencing methods is generally recommended.

Working Group Recommendations, Emerging Renal Cancer Types:

- Consistent morphology and molecular findings support eosinophilic solid and cystic RCC as a distinct tumor type
- There is growing, strong evidence supports RCC with *TFEB* / 6p21 / *VEGFA* amplification as a distinct entity in renal cancer with aggressive behavior
- Other RCC types with *TSC1, TSC2,* or *MTOR* alterations are emerging renal cancer types that may be considered distinctive entities in future classification schemes, including RCC with smooth muscle stroma and eosinophilic neoplasms recently reported
- There is insufficient evidence for recognition of *TCEB1* mutated RCC as a definitive tumor type at present, although this may change with acquisition of more data regarding this emerging tumor type

- There is some evidence for *ALK* rearranged RCC as a distinct tumor type, particularly in view of potential targeted therapy; however, multiple histologic patterns have been recognized

Metastatic renal cancer

Currently, a specific role for molecular pathology in metastatic renal cancer has not been definitively established. (4) However, at the experimental level, genetic profiling of metastatic renal cancer may be considered by clinicians when formulating treatment plans. The most relevant decision for the pathologist in metastatic renal cancer is to attempt to determine clear cell vs non-clear cell renal cancer, which has different preferred treatment regimens. (4) As noted previously, a helpful surrogate for the surgical pathologist is immunohistochemical staining for carbonic anhydrase IX; (16–21) however, the limitations of this marker must be kept in mind, as staining can be decreased or absent in poorly-differentiated clear cell RCC tumors (238) and non-renal tumors can also be positive. (18) Of course, molecular pathology can be utilized in attempting to confirm clear cell vs non-clear cell metastatic renal cancer, such as sequencing studies evaluating *VHL* gene alterations. Although FISH for chromosome 3p deletion may be used as a surrogate, (239, 240) some studies have found 3p loss to be not entirely specific for clear cell RCC, since they can be seen in 6p21 / *TFEB* amplified tumors, papillary RCC with clear cell changes, and unclassified RCC. (11–13) As found in the survey data, it appears that few pathologists are using such molecular techniques extensively in current diagnostic practice.

If comprehensive genomic profiling studies are requested by the oncologist in the setting of metastatic renal cancer, genes that may be relevant to modifying or confirming the treatment plan could include clear cell RCC-associated genes, such as *VHL, BAP1, ARID1A, PBRM1,* and *SETD2*, or genes involved in other pathways, such as the MTOR pathway, like *TSC1*, *TSC2*, *PIK3CA*, and *MTOR*. (241, 242) Secondly, immune checkpoint inhibitors have begun to establish a role in renal cancer. (4, 243) However, since multiple antibody clones currently exist with varying scoring systems for different cancers, the role of pathologic assessment for PD-L1 status in renal cancer remains incompletely understood at present. (243) Nonetheless, treatment with checkpoint inhibitor therapy is gaining traction as a therapeutic option, particularly in clear cell RCC, including a role in national guidelines, but also in some scenarios for non-clear cell RCC. (4, 244–247) Despite the currently limited role of molecular pathology in metastatic RCC, this is an area of tremendous exploration and it is possible that this role will expand significantly in the future.

Summary

Molecular pathology has dramatically influenced our understanding of renal cancer and continues to reshape and elucidate new diagnostic entities. However, knowledge of the genetics of renal cancer subtypes gained from the research setting can often be translated to the diagnostic setting through relatively simple surrogates, including histologic pattern, immunohistochemistry, and copy number analyses, precluding the need for extensive molecular evaluation in diagnostic practice. With the continued explosion of knowledge in molecular pathology of cancer, genetics will doubtlessly have a major impact in

classification and possibly in prognostication and treatment selection for RCC going forward.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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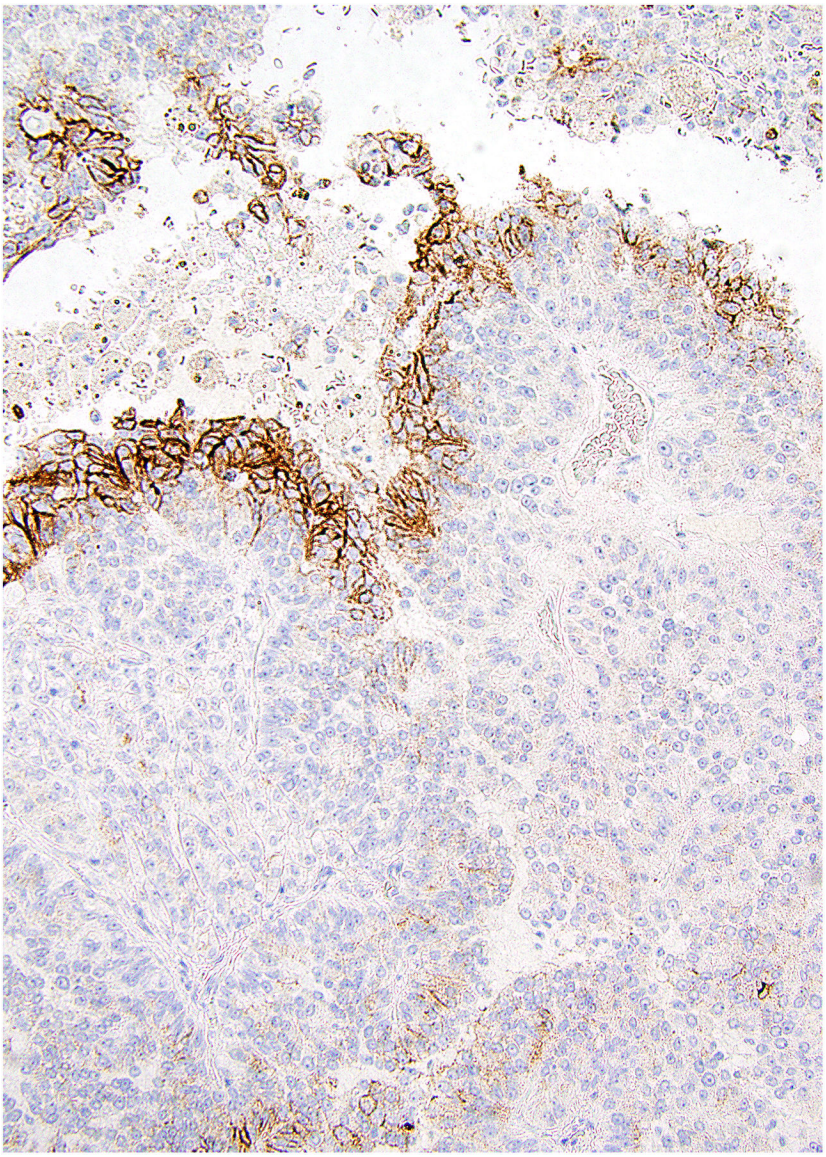
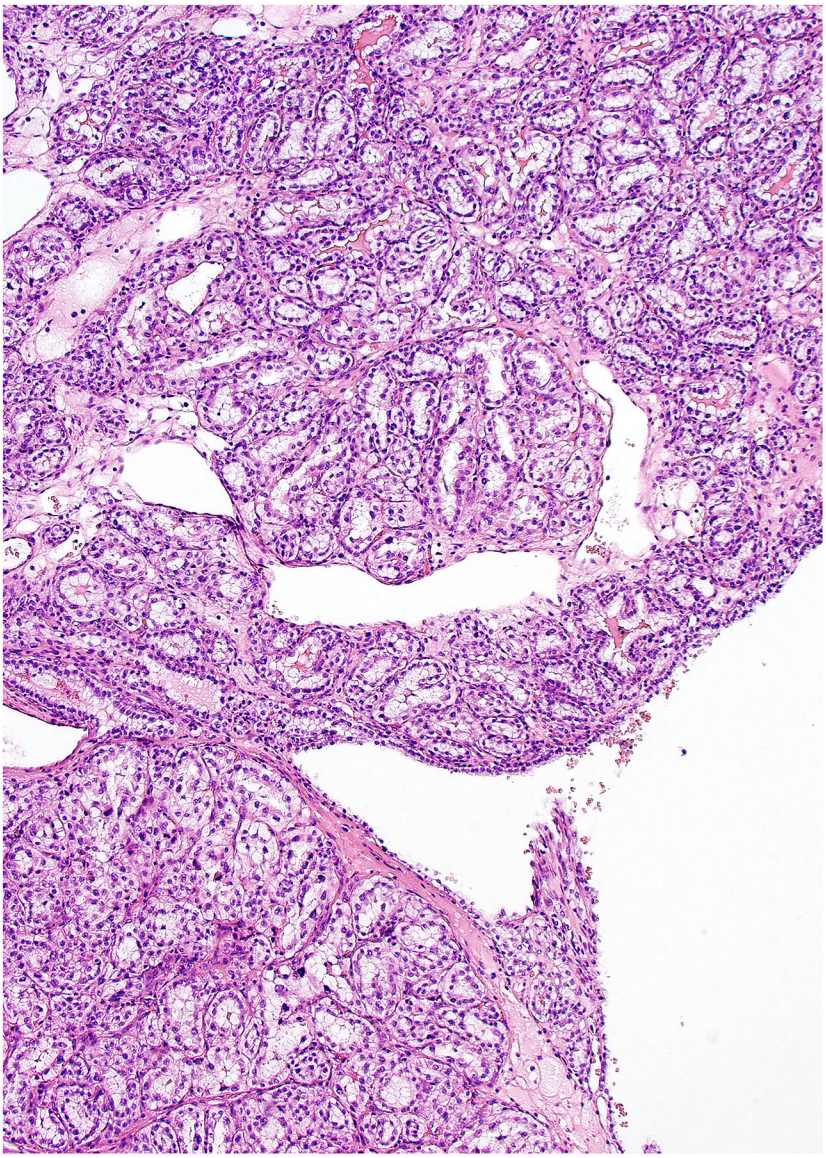


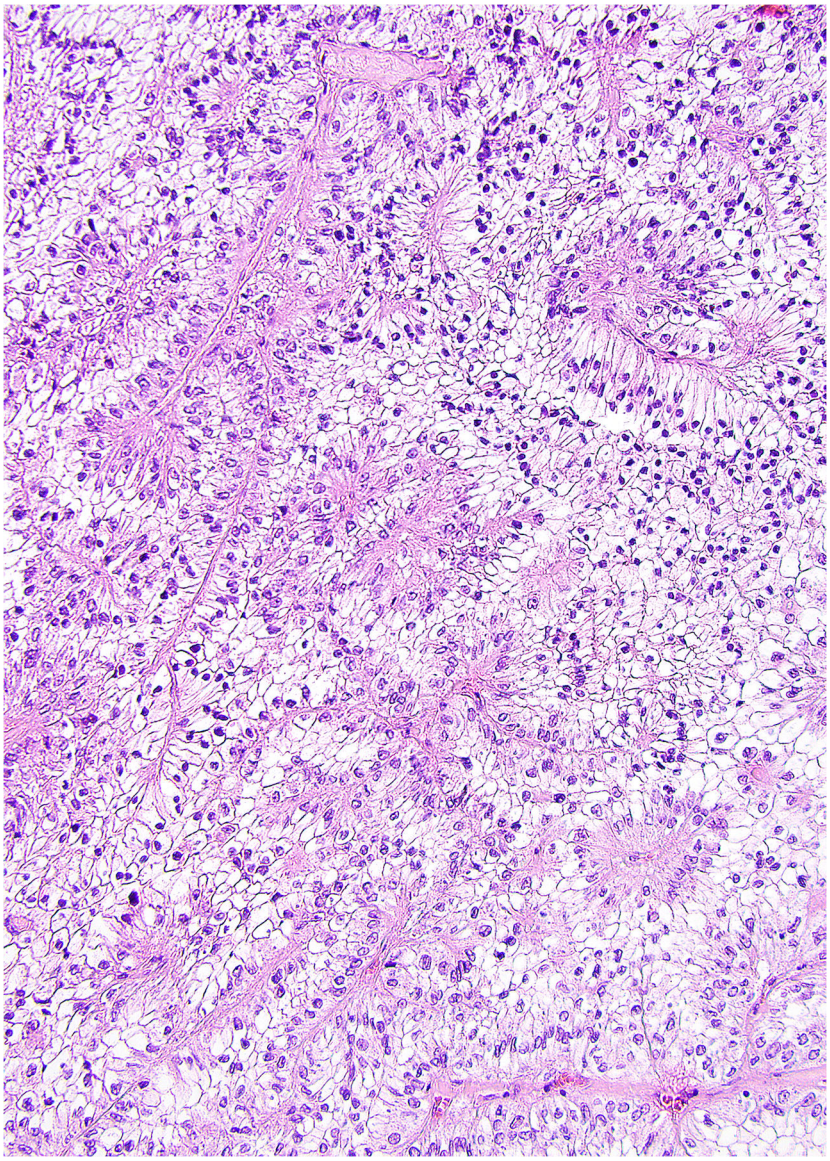
1.

Although a diffuse membranous pattern of carbonic anhydrase IX staining usually would support a diagnosis of clear cell RCC, focal staining can be encountered in the setting of hypoxic or necrotic tissues. This papillary RCC has focal staining only at the edges of the papillary structures.



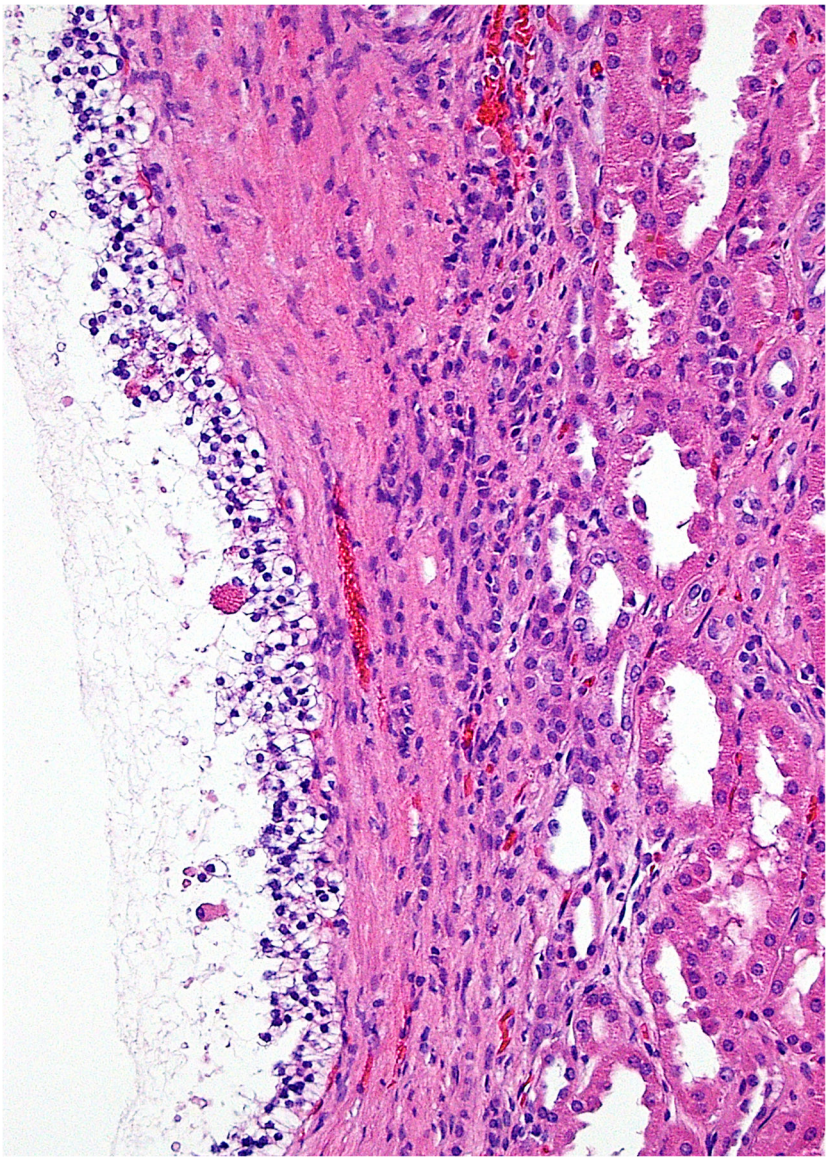
2.

Clear cell papillary RCC is composed most often of branched glandular structures with cells possessing clear cytoplasm. The nuclei are often aligned away from the basement membrane.



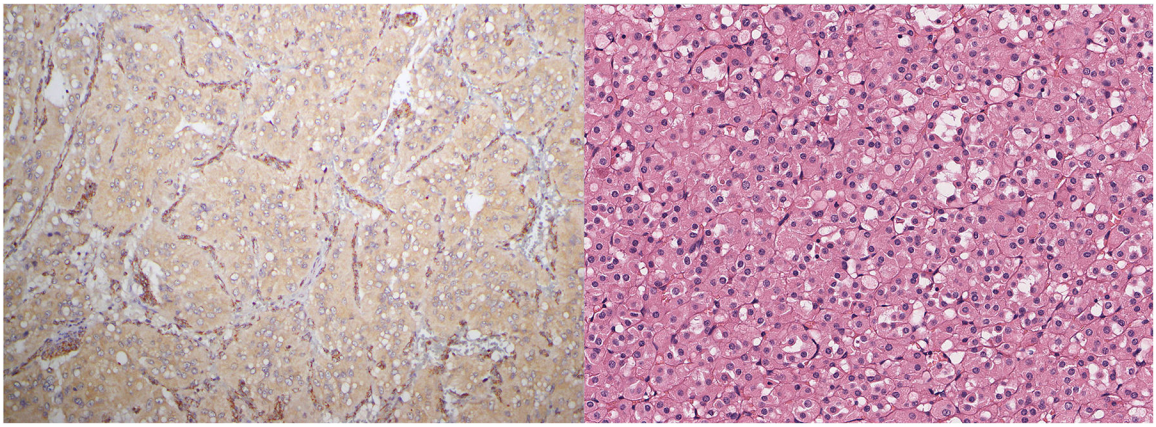
3.

This translocation-associated RCC has *NONO-TFE3* fusion, which may exhibit nuclear alignment, similar to that of clear cell papillary RCC, although often with higher nuclear grade. FISH can show a subtle rearrangement pattern or it can be false-negative due to the close proximity of these genes on the X chromosome.



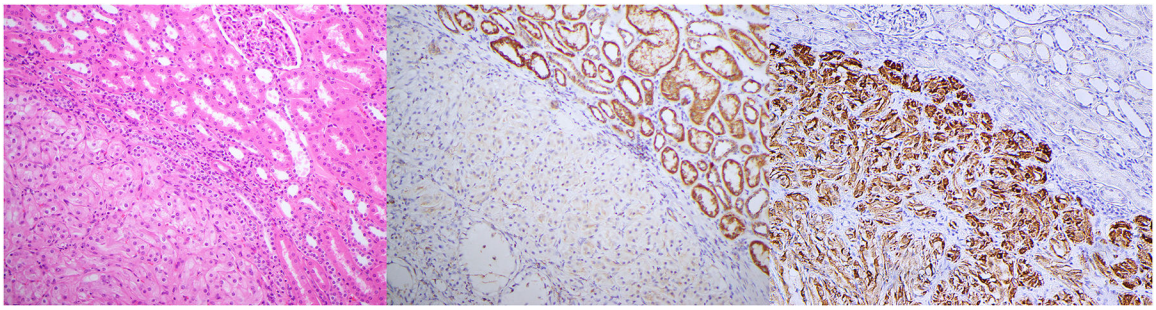
4.

Patients with von Hippel-Lindau disease have multiple clear cell RCC tumors and often renal cysts lined by cells with clear cytoplasm, which are thought to be precursors to neoplasms. This cyst is lined by cells with prominent clear cytoplasm and a slight heaping up of the lining cells.



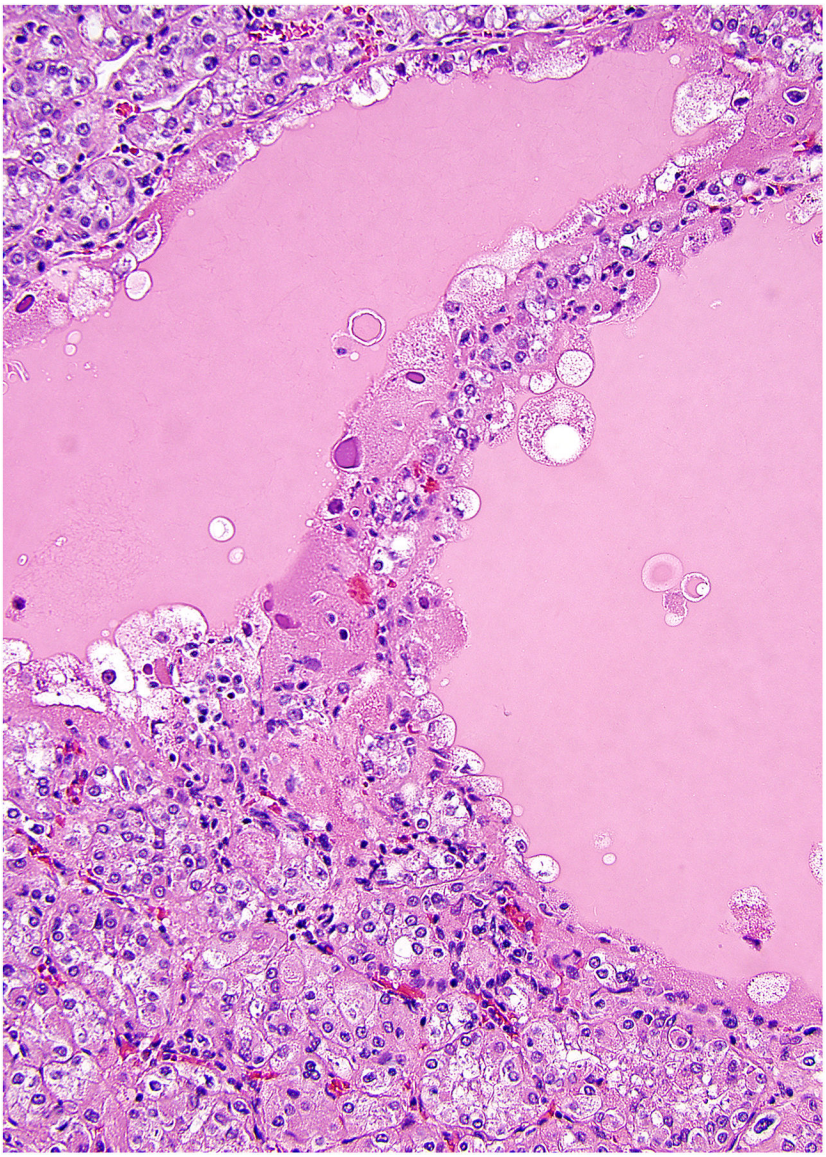
5.

A) Care must be taken in interpreting SDHB immunohistochemistry. In this paraganglioma associated with *SDHD* mutation, the neoplastic cells show a weak diffuse cytoplasmic blush. This is considered SDHB immunohistochemistry 'negative,' as it contrasts strongly with the strong granular cytoplasmic (mitochondrial) staining in the internal positive controls provided by endothelial cells. B) SDH-deficient renal cell carcinoma showing typical features exhibits intracytoplasmic vacuoles/inclusions.



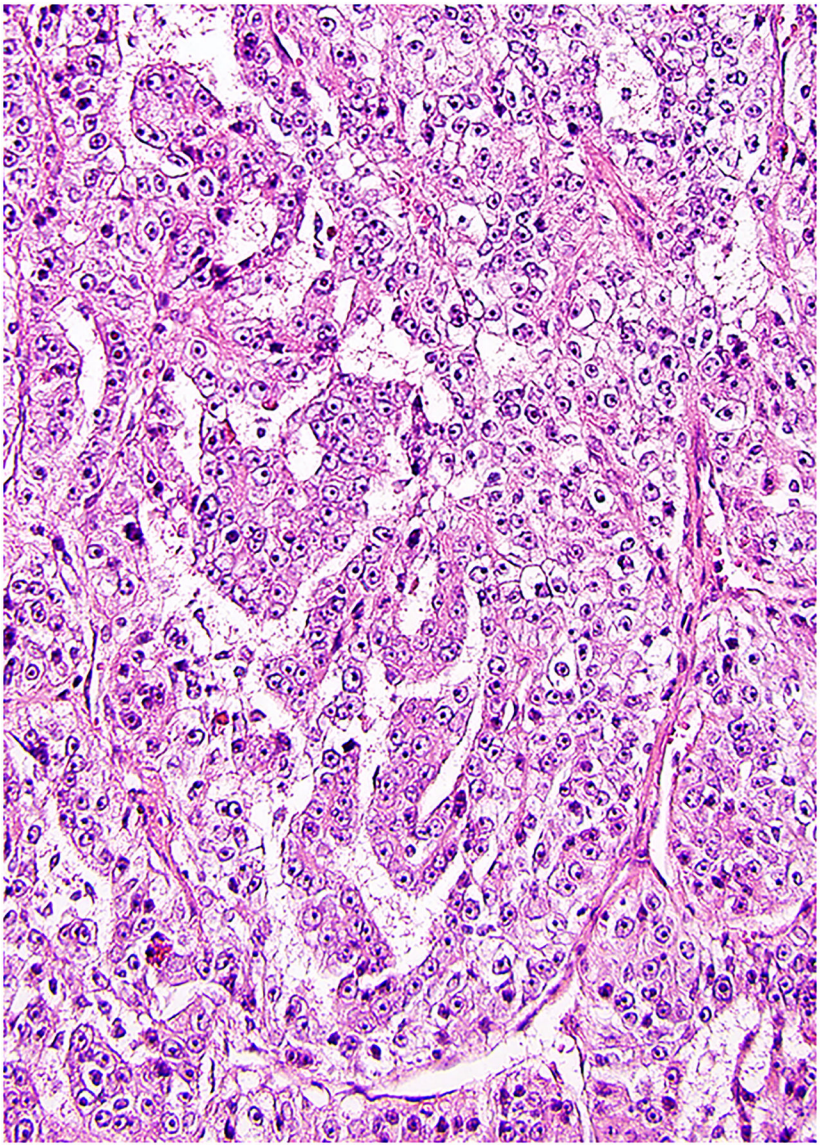
6.

Serial sections of an FH-deficient RCC stained with A) H&E, B) fumarate hydratase, and C) 2SC immunohistochemistry. A) In this case the neoplastic cells have prominent nucleoli but lack the typical papillary or tubulocystic-like architecture of more readily recognized FH-deficient RCC. B) FH immunohistochemistry shows negative staining in all neoplastic cells that contrasts with the positive granular cytoplasmic (mitochondrial) staining in the internal positive controls. C) 2SC immunohistochemistry is positive in a nuclear and cytoplasmic pattern in all the neoplastic cells.



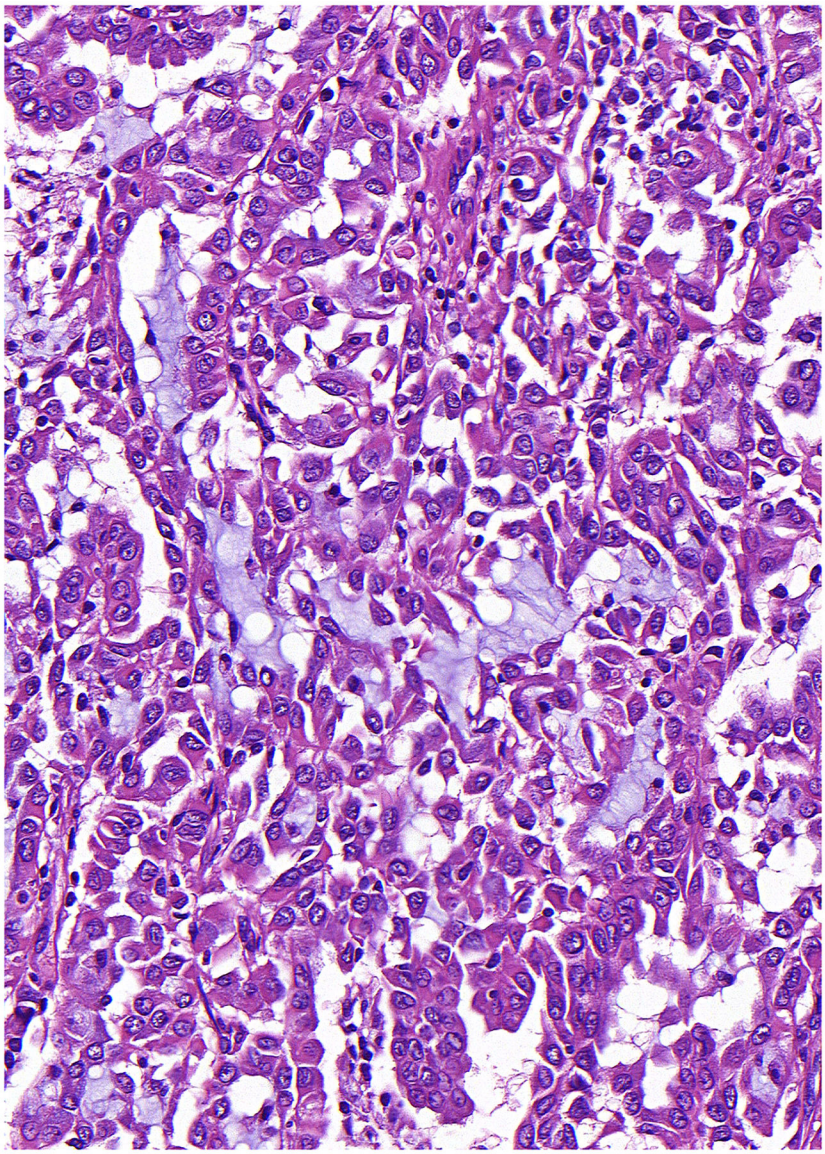
7.

Eosinophilic solid and cystic RCC has been recently recognized to be composed of cells with voluminous eosinophilic cytoplasm, often containing granular basophilic stippling of the cytoplasm. Cysts are lined by cells with similar cytology.



8.

RCC with amplification of *TFEB* / 6p21 / *VEGFA* often has a papillary-like morphology, composed of clear or eosinophilic cells with prominent nucleoli, although it can exhibit multiple histologic patterns. These tumors appear to be highly aggressive.



9.

RCC with *ALK* gene rearrangement has been noted to contain mucin or myxoid material in a subset of cases. This tumor was found to have rearrangement between *ALK* and *TPM3*.

Table 1:

Working Group Members and Organizing Committee

Pedram Argani	**Chair**
Ondrej Hes	Chair
Ying-Bei Chen	Member
Anthony J. Gill	Member
Sean R. Williamson	Member
Lars Egevad	Organizing Committee
David J. Grignon	Organizing Committee
Glen Kristiansen	Organizing Committee

Table 2:

Tools for recognition of MIT family translocation-associated RCC

- Clinical:
  - Young age raises suspicion (but occurrence in age 50+ may be more common due to rarity of RCC in young patients)
- Morphology:
  - Mixture of clear and eosinophilic cells
  - Mixture of papillary and nested architecture
  - Psammoma bodies
  - Hyalinized stroma
  - Unusually voluminous cytoplasm
  - Pigment deposition
- Immunohistochemistry:
  - TFE3 or TFEB protein – strong nuclear labelling in a clean background (but can be technically challenging)
  - Carbonic anhydrase IX – minimal or negative staining
  - Melanocytic markers – often positive
  - Cathepsin K – often positive (but depends on gene fusion)
  - Cytokeratin or vimentin – may be minimal or decreased (but variable)
- Molecular:
  - Break-apart FISH – will detect most rearrangements (but certain fusions by chromosomal inversion may be subtle or false-negative)
  - Polymerase chain reaction or next generation sequencing – will detect rearrangements with false-negative FISH (depending on method, may require knowledge of both partners)