Histological (Sub)Classifications and Their Prognostic Impact in Renal Cell Carcinoma

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Abstract

Renal cell carcinoma (RCC) includes malignant epithelial tumors of the kidney with varying clinical and pathological presentation. RCC classification considers the originating cell type, histopathological features, staining characteristics, and unique molecular features. While data about the prognostic significance of RCC classification into certain subtypes remains inconsistent, there are several parameters which predict patients' survival independent of the RCC subtype. Among these, local tumor expansion, degree of infiltrative tumor growth, presence of lymph node or distant metastases, and histopathological grade of the tumor are general features routinely assessed as prognostic markers. Increasing knowledge about underlying molecular mechanisms has led to numerous molecular and immunohistochemical markers which developed as potential prognostic factors. In the following chapter, the basis of nomenclature, staging, and grading of RCC and prognostic biomarkers are discussed. Afterward, results regarding the prognostic relevance of histological classification are summarized, followed by detailed description of particular RCC subtypes. Histopathology, immunohistochemistry, and molecular pathology as well as its relevance for prognosis are presented for individual subtypes.

Introduction

Renal cell carcinoma accounts for approximately 4% of all diagnosed cancers in western countries (Siegel et al. 2016). While the majority of RCC are sporadic, several hereditary diseases are associated with higher incidences for the development of RCC. During the last decades, several morphological subtypes have been identified, and classification has been revised accordingly. Terminology to designate certain subtypes refers to characteristics such as cytological, architectural and staining features, and molecular alterations. While clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC) account for over 90% of renal cancers, other subtypes are very rare. Based on the observation that different subtypes are associated with certain clinical presentation and outcomes of patients, precise diagnosis is needed to predict disease progression and treatment response (Hsieh et al. 2017). In general, ccRCC is associated with worse prognosis compared to pRCC and chRCC; however, to date it remains unclear whether histological classification itself can be used as independent prognostic marker.

Due to intratumor and intertumor heterogeneity, RCC presents with heterogeneous clinical outcome of patients. Thus, numerous studies aimed to identify biomarkers with prognostic relevance, as well as with predictive value in order to improve clinical management. There are general prognostic parameters independent of the RCC subtype which have been supported by multiple independent studies. Among them, local tumor expansion, degree of infiltrative growth, and differentiation of the tumor are strong prognostic parameters which are routinely reported by pathologists. With the aim to improve prognostic stratification of patients, studies identified several molecular markers which associate with disease aggressiveness. Most molecules are involved in cell growth (e.g., proliferation and cell cycle markers such as Ki67 and cyclins), migration and invasion (e.g., cell adhesion molecules such as E-cadherin), and other pro-malignant processes. Although various studies supported the prognostic value of these molecules, to date there are no

biomarkers routinely used to predict disease progression. The main reason is the lack of independent prognostic significance when adjusting to known prognostic markers including T-stage and tumor grade (Holger Moch et al. 2016).

In addition to general factors, studies observed prognostic markers within individual subtypes. This includes morphological/architectural parameters, markers of differentiation, or further subclassification within individual subtypes. In this chapter, each subtype is introduced followed by summarizing the current knowledge about general as well as subtype-specific biomarkers.

General Classification of Renal Cell Carcinoma

Nomenclature and Classification

Nomenclature of RCC subtypes is based on histologic features, such as cytoplasmatic and/or architectural patterns (e.g., clear cell RCC or papillary RCC) and histochemical staining characteristics (e.g., in chromophobe RCC), in addition to their anatomical localization (e.g., collecting duct carcinoma and renal medullary carcinoma), resemblance to embryological structures, or association with a background renal disease (e.g., acquired cystic disease-associated RCC). Additionally, there are names referring to underlying molecular mechanisms (e.g., MiT family translocation carcinoma, succinate dehydrogenase-deficient renal carcinoma) or familial background (e.g., RCC-associated RCC).

The subtypes differ regarding the originating cell type and partially harbor unique molecular alterations. Histological classification has prognostic value as well as therapeutic relevance.

Staging

According to the current 2016 TNM staging system, there are two categories for renal-limited tumors: pT1a, pT1b, pT2a, and pT2b defined by sizes of $\leq$4, >4- $\leq$7, >7- $\leq$10, and >10 cm, respectively. Regional tumor expansion differentiates spread to peripheral perinephric and central sinus fat as well as renal sinus and vein invasion (pT3a), extension into inferior vena cava below the diaphragm (pT3b) or above the diaphragm or its infiltration (pT3c). Distant spread (pT4) includes direct extension into ipsilateral adrenal gland and invasion of the Gerota fascia (Holger Moch et al. 2016).

Grading

The WHO/International Society of Urological Pathology (ISUP) grading system is recommended for grading RCC (Table 1; see below) (Delahunt et al. 2013). It is a four-tiered grading system and defines grade 1–3 tumors on the basis of their nucleolar prominence. Basis for grading is a single high-power field representing the greatest degree of nucleolar pleomorphism. Presence of pronounced nuclear pleomorphism, tumor giant cells, rhabdoid and/or sarcomatoid differentiation defines a tumor as grade 4 (Holger Moch et al. 2016). Grade 1–4 tumors according to the WHO/ISUP grading system are shown in Fig. 1. The WHO/ISUP grading system is validated as an indicator of prognosis for clear cell and papillary renal cell carcinoma. Due to small numbers of other histological subtypes, it is not (yet) validated as an indicator for their prognosis, but can be applied for these to describe their morphological features.

Table 1 WHO/ISUP grading system for ccRCC and pRCC (Delahunt et al. 2013)

Grade	Description
Grade 1	Nucleoli are absent or inconspicuous and basophilic at ×400 magnification
Grade 2	Nucleoli are conspicuous and eosinophilic at ×400 magnification and visible but not prominent at 100× magnification
Grade 3	Nucleoli are conspicuous and eosinophilic at ×100 magnification
Grade 4	There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation

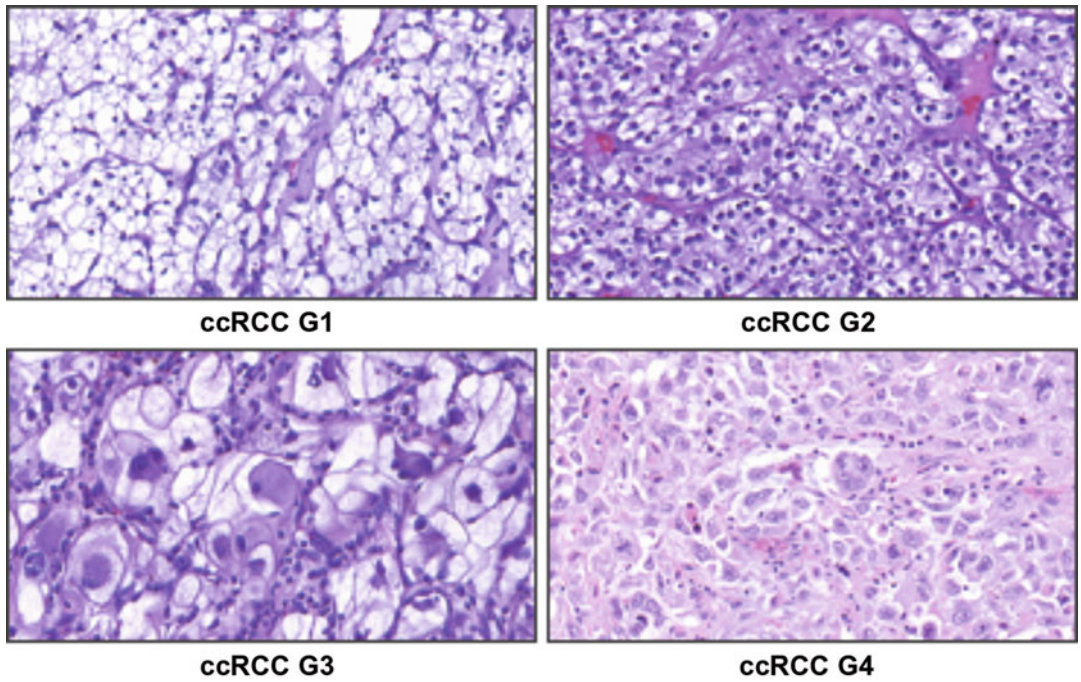

Fig. 1 Representative grade 1–4 tumors according to the WHO/ISUP grading system for renal cell carcinoma

General Prognostic Markers

The most important and routinely used prognostic markers for RCC include TNM stage and grading of the tumor.

Independent of the subtype, prognosis correlates with stage of disease and histopathological grade. Anatomical and histological information with prognostic relevance include tumor size, adrenal involvement, presence of lymph node or distant metastases, sarcomatoid features, (micro-)vascular invasion, tumor necrosis, as well as invasion of the collecting system and the venous system and into the perirenal fat (Holger Moch et al. 2016).

In general, the presence of sarcomatoid differentiation is associated with a dismal prognosis, meaning the tumor is undergoing dedifferentiation into spindle cells. Sarcomatoid differentiation is represented in the grading system as G4, and its presence should be reported for each subtype. Consequently, the separate category for "sarcomatoid renal cell carcinoma" is no longer part of the WHO classification (Hirsch et al. 2015).

Over the past years, the prognostic importance of renal sinus invasion has been established. Patients whose tumors invade the renal sinus have a significantly worse cancer-specific survival than patients with confined tumors. Involvement of the renal sinus increases with increasing tumor size (Lohse et al. 2015).

As mentioned above, WHO/ISUP grading system is validated as an indicator of prognosis for clear cell and papillary RCC, but not for other subtypes (Holger Moch et al. 2016) due to their low frequency.

Recently, the growing understanding of underlying molecular mechanisms of RCC has led to the identification of molecular markers to predict outcome and response to specific treatment approaches. Additionally, signaling pathways revealed to be critically involved in RCC pathogenesis enabled the development of targeted therapy for patients. There are numerous studies investigating the prognostic value of these molecules; however, so far there is no routinely used marker to predict outcome of patients.

Carbonic Anhydrase IX

Carbonic anhydrase IX (CAIX) is a VHL-dependent enzyme induced by hypoxia and critically involved in maintaining cellular pH balance (Neri and Supuran 2011). Loss of CAIC is associated with high-grade tumors, and underexpression in RCC tissue correlates with worse recurrence-free, disease-specific, and overall survival of patients (Genega et al. 2010; Ingels et al. 2017). In addition, high CAIX staining correlates with greater likelihood of response to systematic therapy for patients with metastasized RCC (Stillebroer et al. 2010). A recently published meta-analysis supported CAIX to be a useful prognostic parameter (van Kuijk et al. 2016). Until now, data show conflicting results regarding its significance as independent prognostic marker in multivariate analyses (Leibovich et al. 2007; Zhang et al. 2013); thus CAIX evaluation is not recommended as a useful biomarker.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor plays a crucial role in RCC tumorigenesis and has therefore been investigated as prognostic marker. Several studies observed a significant correlation between VEGF levels in tissues or serum and aggressive phenotypes; however, multivariate analysis could not support these results (Jacobsen et al. 2000; Phuoc et al. 2008).

Cell Cycle Proteins

Analysis of Ki67 and other cell cycle-regulating proteins such as cyclins or p53, reflecting proliferative behavior of the tumor, has been investigated to be used as prognostic factor for RCC. Several studies observed that the level of aberrantly expressed proliferation and cell cycle markers associates with aggressive phenotypes of RCC (Gayed et al. 2013; Haddad et al. 2017). High Ki67 independently predicts reduced disease-free survival time (Dudderidge et al. 2005) and has been suggested to improve clinical management of patients (Xie et al. 2017).

Cell Adhesion Proteins

The cell adhesion protein E-cadherin inversely correlates with the aggressive phenotype of various epithelial cancers. In RCC, loss of E-cadherin associates with increased incidence of metastasis (Katagiri et al. 1995). In ccRCC, aberrant nuclear E-cadherin has been suggested as prognostic marker in the background of VHL mutation (Gervais et al. 2007) and reduced expression has recently been identified to predict disease recurrence (Haddad et al. 2017). Recently, the adhesion molecule EpCAM (epithelial cell adhesion molecule) has renewed interest as independent studies revealed its positive expression as predictor for improved survival in both localized (Seligson et al. 2004; Eichelberg et al. 2013) as well as in metastasized RCC (Kim et al. 2005). While the majority of papillary and chromophore RCC samples showed an at least weak staining, in ccRCC EpCAM is lost in a subset of tumors which is associated with high-grade disease (Eichelberg et al. 2013; Zimpfer et al. 2014). Epithelial membrane antigen (EMA, MUC1) is a membrane-associated mucin reported to associate with poor prognosis in RCC (Langner et al. 2004) and to be expressed in carcinomas with sarcomatous differentiation (Yu et al. 2017).

Epithelial-Mesenchymal Transition (EMT) Markers

Vimentin as mesenchymal marker is widely used as diagnostic marker in various cancer types. ccRCC and most papillary RCCs are usually positive for vimentin, and high expression in ccRCC correlates independently with poor survival using different endpoints (Ingels et al. 2017; Shi et al. 2015). Among other epithelial-mesenchymal transition (EMT) markers, it has been shown that Clustering and Twist predict outcome in clinically localized RCCs (Harada et al. 2012). More studies are needed to validate

the independent prognostic value of EMT markers such as vimentin and proof their sensitivity and specificity for routine use.

Immune-Mediating Proteins

The preoperative measurement of circulating immune-mediating proteins such as C-reactive protein (CRP) or osteopontin has been suggested as prognostic markers for RCC patients (Sim et al. 2012). However, recommendations as routinely used marker are incongruent as CRP might not improve reductive accuracy (Bedke et al. 2012). In tissues, high CRP expression associates with poor survival in univariate analyses (Can et al. 2014). Overall, most studies focus on serum levels of CRP rather than intratumoral CRP expression, thus conclusion regarding assessment on tissues are limited.

Prognostic Relevance of Histological Classification

Numerous studies give evidence that prognosis is dependent on histological classification. Using large cohorts, several studies reported that ccRCC is generally associated with worse outcome of patients compared to papillary and chromophore CCC (Amin et al. 2002; Cheville et al. 2003; Patard et al. 2005). Observing an independent prognostic value, authors highlighted the need for accurate subtyping. As a representative example, Cheville et al. reported 5-year cancer-specific survival rates of 68.9%, 87.4%, and 86.7% for patients with clear cell, papillary, and chromophobe RCC, respectively, by including 2385 patients in their study. Additionally, several studies observed that ccRCC is associated with higher grades and advanced TNM stages compared to papillary RCC (Gudbjartsson et al. 2005). However, results are incongruent as multivariate analyses adjusting to tumor stage and differentiation partially failed to reveal significant differences in outcome between histological subtypes (Patard et al. 2005; Schrader et al. 2009).

Histological Subtypes of Renal Cell Carcinoma

Clear Cell Renal Cell Carcinoma (ccRCC)

Definition

Clear cell renal cell carcinoma (ccRCC) accounts for 65–70% of all renal cancers and occurs predominantly sporadically. In most cases, ccRCCs are solid tumors in the renal cortex, while multifocal and/or bilateral manifestation occurs in less than 5% of cases and is associated with hereditary cancer syndromes (Holger Moch et al. 2016).

Macroscopy

Macroscopically, tumors are well circumscribed and separated from the kidney by a pseudo capsule, while a real capsule is usually lacking. Diffuse infiltration in the renal parenchyma is untypical. The golden-yellow cut surface represents the high lipid content of tumor cells. Tumors harbor different grades of necrosis and hemorrhage and to a lesser extent calcifications and ossifications (Holger Moch et al. 2016).

Different metastatic spreads of ccRCCs lead to metastases on unusual sites. ccRCCs metastasize predominantly hematogenously via renal veins and the vena cava, resulting in pulmonary metastases. To a lesser extent, metastases in the central nervous system, head and neck region, and central and peripheral bones result from tumor spread into the lumbar veins. Lymphatic metastases can affect hilar, aortic, caval, and thoracic nodes (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

ccRCCs show diverse architectural growth patterns, mostly solid alveolar and acinar patterns which might appear micro- or macrocystic through dilatation of alveolar or acinar structures. Less often, tubular or pseudopapillary growth patterns as well as fibromyxoid stroma areas, calcification, and ossification might be seen. In more aggressive phenotypes, sarcomatous and rhabdoid changes have been described. Characteristically, tumors contain typical small, thin-walled vessel

formations as well as little inflammatory responses. Beside heterogenous morphologies, tumors are characterized by cells with clear or eosinophilic cytoplasm and distinct cell membranes. Eosinophilic cytoplasm is associated with high-grade tumors and predominantly present in necrosis or hemorrhage. Nuclei of tumor cells are mostly round with evenly distributed chromatin. In high-grade ccRCC, bizarre and large nuclei might be seen, and nucleoli range from small to large (Holger Moch et al. 2016).

PAX8 is a sensitive marker for the detection of renal epithelial neoplasms and is expressed in the nucleus of virtually all ccRCCs. Evaluation of PAX8 expression revealed higher intensity in RCC metastatic sites compared to the primary tumor (Barr et al. 2015). Additionally, ccRCCs show a positive reaction against epithelial markers such as AE1/AE3 or CAM5.2. Carbonic anhydrase IX (CAIX) is overexpressed in more than 75% of ccRCCs but lost in high-grade tumors. Concordantly, several studies observed that decreased CAIX levels are independently associated with poor survival of patients with advanced ccRCC, suggesting to use CAIX staining as a prognostic marker (Bui et al. 2003). However, other studies with long-term follow-up revealed conflicting results regarding CAIX as independent prognostic biomarker (Zhang et al. 2013). Comparing staining distribution, ccRCCs exhibit a membranous staining pattern of CAIX, while in pRCC, a basolateral staining can be observed. In contrast to chromophobe RCC, which exhibits diffuse CK7 expression, ccRCC lacks CK7, or CK7 is limited to isolated cells especially in high-grade ccRCCs. To distinguish ccRCC from other renal neoplasms, CD10 as a proximal tubule marker might be useful. The mesenchymal marker vimentin is higher expressed in tumors compared to paired normal renal tissue and shows the strongest levels in high-grade areas of ccRCCs. In line with this, vimentin has been suggested to predict survival of patients (Shi et al. 2015). Additionally, vimentin is a useful diagnostic marker to distinguish ccRCC from chromophobe RCC (Williams et al. 2009).

Besides having frequent molecular alterations, ccRCCs exhibit an inter- and intratumoral heterogeneity which hampers the development of gene-based molecular targets for therapy. ccRCCs possess characteristically loss of 3p promoting tumor initiation, progression, and metastasis. The most common genetic alterations involving the 3p locus are aberrations of the von Hippel-Lindau (VHL) tumor suppressor gene at 3p25–26 (Holger Moch et al. 2016). Different aberrations affecting VHL include promoter region methylation, loss of heterozygosity, and a large number of mutations leading to biallelic genetic alteration in both hereditary and sporadic ccRCCs. The von Hippel-Lindau protein is encoded by the VHL gene and plays a crucial role in the oxygen-dependent ubiquitin-mediated proteolytic degradation of several proteins. Studies show conflicting results regarding VHL gene aberration as prognostic or predictive biomarker (Cowey and Rathmell 2009). In addition to VHL, other genes on 3p frequently lost in ccRCC include epigenetic regulators and chromatin remodeling complexes such as SETD2, BAP1, and PBRM1, which are characterized as two-hit tumor suppressor genes. Among them, Polybromo 1 (PBRM1) is the second most frequently lost tumor suppressor gene in ccRCC with a mutation rate of approximately 45%. PBRM1 encodes BAF180 which is crucially involved in nucleosome remodeling and regulates oncogenic features of tumor cells (Brugarolas 2014). The BRCA1-associated protein-1 (BAP1) gene is mutated in approximately 15% of ccRCCs and encodes the protein BAP1, which is involved in the PI3K and mTOR signaling. BAP1 loss is associated with high-grade tumors and ccRCC-associated death of patients. In the majority of cases, PBRM1 and BAP1 mutation occur in a mutually exclusive manner, while tumors harboring mutations in both BAP1 and PBRM1 seem to possess an aggressive phenotype (Brugarolas 2014). Other molecular alterations comprise allelic losses on 14q partly resulting in loss of HIF1A, which has been suggested to be a molecular subtype of ccRCC and associates with poor prognosis (Monzon et al. 2011). A high proportion of ccRCCs harbors gain of 5q leading to amplification and subsequent overexpression of the SQSTM1 oncogene (Li et al. 2013).

The most precise prognostic and predictive factor for patients with ccRCC is the pathological stage, followed by tumor grade according to the WHO/ISUP grading system, and differentiation reflected by the presence of tumor necrosis, sarcomatoid, and rhabdoid features. Importantly, immunohistochemical and molecular markers described above are not routinely used in clinical practice.

Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Definition

Multilocular cystic renal neoplasms of low malignant potential account for less than 1% of all renal tumors and characteristically do not recur or metastasize. Molecular analyses suggest that this neoplasm is genetically related to ccRCC. Most tumors are discovered incidentally and are associated with excellent prognosis (Holger Moch et al. 2016).

Macroscopy

The tumor is composed of numerous variably sized cysts and separated by thin septa, while solid tumor nodules are absent (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

Multilocular cystic renal neoplasms of low malignant potential are morphologically not distinguishable from low-grade ccRCC. Cysts are lined by a single layer of clear cell tumor cells without prominent nucleoli, conform to WHO grade 1 or 2. Tumor cells express PAX8 and carbonic anhydrase IX. The septa between cysts consist of fibrous tissue characteristically with clusters of tumor cells. Tumor necrosis, vascular invasion or sarcomatous features are absent. Molecular alterations are similar to ccRCCs, including VHL mutations and 3p deletions (Holger Moch et al. 2016).

Papillary Renal Cell Carcinoma (pRCC)

Definition

Papillary renal cell carcinoma (pRCC) is a malignant tumor deriving from renal tubular epithelium. It is the second most common subtype of RCCs in adults and the most common subtype observed in pediatric RCC, accounting for approximately 10% of renal epithelial neoplasms (Fernandes and Lopes 2015). It occurs often in kidneys with end-stage renal disease and is rarely associated with hereditary syndromes. Traditionally, there are two types of pRCC: types 1 and 2 (Holger Moch et al. 2016).

Macroscopy

Most tumors are well circumscribed with a pseudo capsule and occur in the renal cortex, in part in association with renal scarring. If it occurs multiple and/or bilateral, an association with hereditary pRCC syndrome is possible (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

pRCC shows papillary or tubulopapillary architecture with papillae formed by fine fibrovascular cores, often containing foamy macrophages and small calcifications (psammoma bodies).

Histologically, papillae of type 1 carcinoma show cells with nuclei in a single layer, with pale scanty cytoplasm. Cells of type 2 carcinoma show nuclear pseudostratification, abundant eosinophilic cytoplasm, and a lesser differentiation with a higher nuclear grade. Type 2 pRCC is usually larger and advanced and displays necrosis and lymphovascular invasion more frequently compared with type 1 pRCC. Type 2 pRCC can present with extensive nodal metastasis (Holger Moch et al. 2016). An example of pRCC types 1 and 2 is shown in Fig. 2.

The variant oncocytic pRCC (opRCC) shows eosinophilic, finely granular cytoplasm with prominent nuclei. There are statements that opRCC might be classified as an independent subtype of pRCC. It tends to be a favorable subtype mimicking type 1 pRCC with low malignant

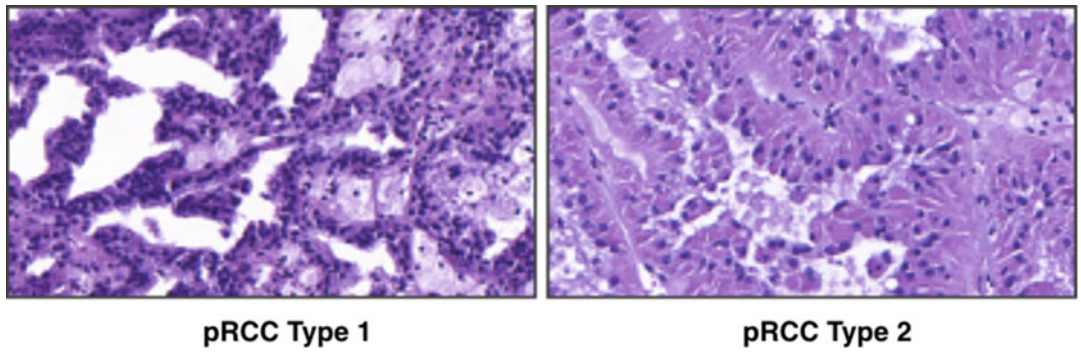

Fig. 2 Histology of papillary renal cell carcinoma type 1 and 2

potential and same genetic features (Han et al. 2017).

In both types, sarcomatous or rhabdoid differentiation is associated with dismal prognosis, while necrosis instead does not seem to predict survival of patients (Peckova et al. 2017).

Based on genomic analysis, there is evidence that type 1 and type 2 pRCC are individual diseases which differ biologically and clinically (Cancer Genome Atlas Research N et al. 2016). Therefore, pRCC subtyping is an independent predictor of outcome.

Type 1 tumors associate with significant better survival of patients as well as with lower stage and grade compared to type 2 pRCC. Type 1 frequently harbors gains of 7p and 17p, loss of the Y chromosome, and additional gains (3q, 8p, 12q, 16q, and 20q (Fernandes and Lopes 2015)) as well as alterations in the MET pathway (Cancer Genome Atlas Research N et al. 2016).

Type 2 pRCC instead shows allelic imbalance of one or more of 1p, 3p, 5p, 6p, 8p, 9p, 10p, 11p, 15p, 18p, and 22p. Losses of 8p, 9p, and 11q are associated with higher T stage and higher clinical stage, loss of 8p with positive M stage, and loss of 9p and gain of 3q with positive N stage (Fernandes and Lopes 2015). Molecular analysis could show that type 2 papillary RCC is a heterogeneous disease which can be divided in at least three further subgroups: tumors with CDKN2a alterations, TFE3/TFEB fusions, and CIMP hypermethylations. Tumors with CDKN2A loss and CpG island methylator phenotype (CIMP) are associated with a poor prognosis (Fernandes and Lopes 2015).

pRCC shows positive reactions for cytokeratin AE1/AE3, CAM5.2, high-molecular-weight cytokeratins, EMA, AMACR, RCC, vimentin, CD10, and CK7; CK7 is more in type 1 than in type 2.

Several genetic syndromes are associated with pRCC. Hereditary pRCC syndrome is an early-onset form which has recently been reported with multiple and/or bilateral Type 1 pRCC. It is based on the detection of germline mutations of the c-MET gene, associated with additional tumors in the breast, pancreas, lung, skin, and stomach (Fernandes and Lopes 2015). It is well accepted as a specific class of inherited renal cancer with an autosomal dominant pattern of inheritance and incomplete penetrance (Fernandes and Lopes 2015).

Hereditary Leiomyomatosis and Associated Renal Cell Carcinoma

Definition

Hereditary leiomyomatosis and associated renal cell carcinoma (hlRCC) is a genetic syndrome based on activating mutations in FH gene at 1q42.3-q43, which encodes the enzyme fumarate hydratase (Holger Moch et al. 2016).

Macroscopy

Renal tumors are predominantly localized in the cortex, but the medulla can be affected as well. It is associated with cutaneous leiomyomas, mostly located on arms or thorax, as well as uterine leiomyomas (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

A renal tumor associated with hlRCC is mostly papillary, but there can also be a morphologic overlap with collecting duct carcinoma. Tumor cells show large nuclei with prominent inclusion-like eosinophilic nucleoli and abundant eosinophilic cytoplasm, resembling type 2 pRCC. The nucleoli are often surrounded by a clear halo, which imparts a "viropathic-like" appearance (Holger Moch et al. 2016).

Leiomyomas in context of hlRCC show atypical features with nuclei similar to those in renal tumors such as perinuclear halos (Przybycin et al. 2013).

Due to the underlying mutation of the FH gene, it shows a negative reaction for fumarate hydratase and positive reaction for modified cysteine-S-(2-succino)cysteine.

Prognosis is poor, and tumors frequently present at high stage with perinephric and/or venous invasion (Przybycin et al. 2013). There is a tendency toward early widespread dissemination, even with small tumors. hlRCC-associated renal tumors are estimated to be more aggressive than renal tumors of other hereditary renal cancer syndromes (Schmidt and Linehan 2014).

The subgroup of type 2 pRCC with CIMP hypermethylation patterns shows germline or somatic mutation of the FH gene, too, which could be one reason for poor prognosis of hlRCC (Cancer Genome Atlas Research N et al. 2016).

Chromophobe Renal Cell Carcinoma (chRCC)

Definition

Chromophobe renal cell carcinoma (chRCC) is a malignant renal tumor, arising from the distal nephron. It is characterized by cells with prominent cell membranes, wrinkled (raisinoid-like) nuclei with perinuclear halos, and pale to eosinophilic cytoplasm. It accounts for 5–7% of RCCs and is mostly sporadic. Hereditary forms are known, especially in the context of the Birt-Hogg-Dubé syndrome (Holger Moch et al. 2016).

Macroscopy

chRCC presents as well-circumscribed and unencapsulated tumor, light tan to brown in color, and sometimes with a central scar (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

In its classic form, chRCC shows predominantly large pale cells (>80%) with a reticulated cytoplasm and distinctive cell membranes. This form is associated with necrosis and sarcomatous changes and presents as an aggressive tumor with a high potential for distant metastases (Holger Moch et al. 2016). An example of chRCC is shown in Fig. 3.

In its eosinophilic variant (> 80% eosinophilic cells), there are predominantly smaller, eosinophilic cells. This variant shows similarities to

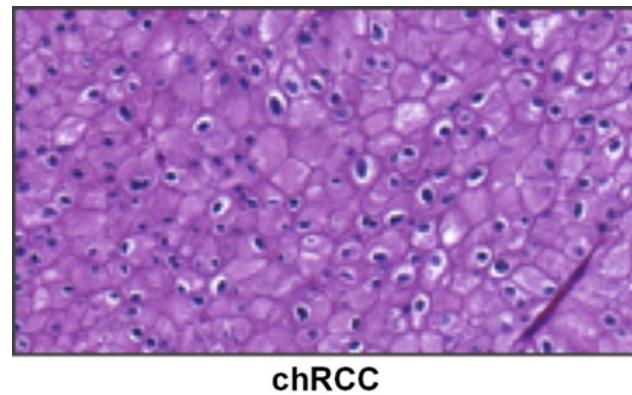

Fig. 3 Histology of chromophobe renal cell carcinoma

oncocytomas. It is often bilateral (11%) and multifocal (22%). Nuclei show an irregular wrinkled (raisinoid-like) appearance with perinuclear halos and a coarse chromatin; sometimes there is a binucleation. The growth pattern is solid, at times tubulocystic, with broad fibrotic septa (Vera-Badillo et al. 2012).

There are also mixed types. There is no evidence that the histologic variants show different molecular alterations.

Most cases are low grade and low stage (confined to the kidney) and show a favorable prognosis; the 5-year survival rate is estimated as 78–100%. Even in the setting of metastatic disease, chRCC has a better prognosis than pRCC and a similar prognosis to ccRCC, with a median survival of approximately 29 months compared with 5.5 months in pRCC (Motzer et al. 2002).

The small subset behaving aggressively is associated with a higher tumor stage, sarcomatous differentiation, necrosis, and small vessel invasion. Renal vein invasion is seen in approximately 5% of cases and incidence of metastatic disease is 6–7% (Vera-Badillo et al. 2012). Despite this more aggressive subset, there is no grading indicated (Hirsch et al. 2015).

Tumors show positive reactions for CD117 (KIT), parvalbumin, kidney-specific cadherin, and CK7. Hale colloidal iron staining is often diffused cytoplasmatically positive.

Cytogenetic studies revealed that chRCC is typically hypodiploid and contains a combination of monosomies involving chromosomes 1, 2, 6, 10, 13, and 21 (Hirsch et al. 2015). Losses of 2, 10, 13, 17, and 21 have been described in 93%, 93%, 87%, 90%, and 70% of chRCC, respectively, and might be useful as a diagnostic marker (Vera-Badillo et al. 2012).

There is a subset of tumors whose histology shows an overlap between chRCC and oncocytoma, leading to the name "hybrid oncocytoma/chromophobe RCC." Preferentially, this form is associated with the Birt-Hogg-Dubé (BHD) syndrome, a genetic syndrome which is characterized by inactivating mutations in the FLCN gene, which encodes for folliculin. FLCN is located on the short arm of chromosome 17. In FLCN −/− tumors, mTOR is upregulated resulting in activation of both mTORC1 and mTORC2 pathways. The PI3K-Akt-mTOR pathway seems to play a relevant role in preclinical models in this tumor type, and this could explain partial response observed with mTOR inhibitors. However, in sporadic chRCC, losses of chromosome 17 were reported but without associated FLCN mutations (Vera-Badillo et al. 2012).

Tubulocystic Renal Cell Carcinoma (tcRCC)

Definition

Tubulocystic renal cell carcinoma (tcRCC) is an uncommon cystic renal epithelial tumor, accounting for <1% of all RCCs. Less than 100 tcRCC cases have been documented to date in the literature (Holger Moch et al. 2016).

Macroscopy

It typically involves the renal cortex or corticomedullary junction. It probably originates from the proximal convoluted tubule or intercalated cells. The left kidney is more commonly (70%) affected. It mostly presents as a solitary, multicystic, and well-circumscribed mass with a spongy surface (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

As the name implies, tcRCC is built up of numerous tubules of different size admixed with larger cysts which are lined by a single layer of flattened to cuboidal epithelium. The stroma is fibrotic. The nuclei are enlarged and irregular, their nucleoli intermediate to large (WHO grade 3). Cytoplasm sometimes shows oncocytoma-like aspects. It shows positive reaction for AMACR, CD10, CK19, and vimentin (Holger Moch et al. 2016).

Despite its high-grade cytology, most cases of tcRCC reported appear to have a favorable prognosis, usually being localized to the kidney at the time of diagnosis (pT1 and pT2) with <10% showing pT3 features (Zhao et al. 2015a) and with only rare cases of distant metastases (Bhullar et al. 2014), suggesting little value of grading in this neoplasm.

Because of its rarity, there is insufficient knowledge about the reasons for its indolent course.

Collecting Duct Carcinoma (cdCA)

Definition

Collecting duct carcinoma (cdCA) is a rare malignant epithelial tumor arising from the principal cells of the renal collecting ducts of Bellini, accounting for <1% of all RCC. It occurs more frequently in men (2:1) (Holger Moch et al. 2016).

Macroscopy

It is mostly located in the medulla with extension in the cortex or beyond the kidney with poorly defined tumor borders. If the tumor has grown large, the primary lesion can be difficult to identify. In these cases, identification of an infiltrative pattern that extends between nonneoplastic tubules in the cortex can be helpful (Hirsch et al. 2015). Both kidneys are affected equally (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

Histologically, it presents as a tubular, tubulopapillary, or tubulocystic tumor with irregular elongated and branching tubulus. There is a single layer of cells which are cuboidal to columnar or hobnail with pale to clear or eosinophilic cytoplasm. The nuclei are high grade, meaning large and pleomorphic with prominent nucleoli (Holger Moch et al. 2016). Further, there are numerous and abnormal mitoses as well as apoptotic bodies and coagulative necrosis. Sarcomatous and rhabdoid differentiation is commonly seen (Hirsch et al. 2015).

Diagnosis is a diagnosis of exclusion. Diagnostic criteria referred to WHO are (1) a medullary involvement, (2) a predominant tubular morphology, (3) desmoplastic stromal reaction, (4) high-grade cytology, (5) infiltrative growth pattern, and (6) the absence of other RCC subtypes or urothelial carcinoma.

Histological diagnosis is an adverse prognostic factor in itself. cdCA is per definition a high-grade tumor, and as a consequence, a grade should not be assigned (Srigley et al. 2013). The majority shows a highly aggressive clinical course with high prevalence (80%) of metastases and high tumor stage (>70% ≥pT3) at time of diagnosis. Three-year relative survival rates for localized, regional, and distant disease have been reported to be 93%, 45%, and 6%, respectively (Srigley et al. 2013).

Tumor cells show positive reactions for high-molecular-weight cytokeratins and CK7, sometimes a co-expression with vimentin. Immunohistochemical overlap with urothelial carcinoma shows positive reactions for PAX8 in the majority of cases and for p63 in 14% (Srigley et al. 2013).

Cytogenetic reports are limited due to the rarity of this tumor type. Most studies detect a combination of several monosomies, whereas others find more trisomies.

To date, conclusions based on genetic profile regarding prognosis cannot be drawn.

Mucinous Tubular and Spindle Cell Carcinoma (mtsRCC)

Definition

Mucinous tubular and spindle cell carcinoma (mtsRCC) is an uncommon renal epithelial neoplasm accounting for <1% of all RCCs with about 100 reported cases worldwide. It shows a female predominance with a ratio of 3:1. It is believed to be a low-grade malignant renal epithelial tumor based on low histological grade (Wu et al. 2013) with rarely described cases of lymph node metastasis and recurrence (Crumley et al. 2013). An association with nephrolithiasis is described (Holger Moch et al. 2016).

Macroscopy

In general, it occurs in the cortex, but localization in the medulla is possible. It exhibits as a well-circumscribed tumor with solid, shiny, and mucoid cut surface. An origin from proximal nephron has been suggested (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

Histologically, the tumor is characterized by a mixture of tubular and spindle cell components separated by variable amounts of mucinous stroma (Holger Moch et al. 2016).

Histologic features include mucin-poor variants, tumors with either tubular or spindle cell predominance, and oncocytic cytology (Hirsch et al. 2015).

Tumor cells are usually bland appearing with scant, pale to eosinophilic cytoplasm with round, and uniform nuclei that display low nuclear grade. Rare cases with sarcomatoid differentiation characterized by high-grade cytologic atypia, tumor necrosis, and increased mitotic activity have been reported (Zhao et al. 2015b). This dedifferentiation generally has a worse prognosis with shorter disease-free survival as well as early, more frequent metastasis (Arafah and Zaidi 2013). However, cases with classic, low-grade morphology with multiple distant metastases with both the primary tumor and metastases displaying identical morphology have also been reported (Zhao et al. 2015b). Tumor cells show positive reactions for CK7, PAX2, and AMACR and negative reactions for CK7 and AMACR in areas with sarcomatoid differentiation.

The immuno-profile suggests a proximal nephron origin and intimate relationship to pRCC, but unlike pRCC, it lacks gains on chromosomes 7 and 17 and losses of chromosome Y, showing that mtsRCC is a genetically distinctive entity different from pRCC (Zhao et al. 2015b).

Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

Definition

Succinate dehydrogenase-deficient renal cell carcinomas (sdhRCCs) are hereditary malignant tumors defined by loss of succinate dehydrogenase (SDH) B (SDHB) expression, resulting in dysfunction of the mitochondrial complex II. sdhRCCs occur on the background of double-hit inactivation of the tumor suppressor gene SDH by germline mutations, which are associated with tumor syndromes causing paraganglioma, gastrointestinal stromal tumors, and pituitary adenoma. sdhRCCs account for approximately 0.05–0.2% of all renal cell carcinomas and present most commonly in young adult patients (Holger Moch et al. 2016).

Macroscopy

sdhRCCs are well-circumscribed solid or, to a lesser extent, multicystic tumors with a red-brown cut surface. Mostly, tumors are restricted to the kidney, while multifocal or bilateral manifestation occurs in approximately 30% of patients (Holger Moch et al. 2016).

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Microscopically, the tumor appears with lobulated or pushing margin and distributed cysts containing eosinophilic material. Malignant cells grow in a solid, nested, or tubular growth pattern. Characteristically, malignant cells have cytoplasmic vacuoles or inclusions that contain eosinophilic material which might appear bubbly. In high-grade tumors, these characteristics may be less prominent. The chromatin appears flocculent, nuclear contours are smooth, nucleoli are inconspicuous, and chromatin is evenly dispersed. With higher grades, increased nuclear atypia and eventually sarcomatoid features can be observed (Holger Moch et al. 2016).

The diagnosis of sdhRCC is defined by the loss of immunohistochemical staining for SDHB. Positive markers comprise CAM 5.2 and EMA and at least focal PAX8 expression (Williamson et al. 2015). In contrast, cytokeratin is present in only 30% of cases.

The underlying molecular alteration of sdhRCC is a double-hit inactivation of one of the SDH-genes through germline mutations (most commonly SDHB, less commonly SDHC, SDHA, and SDHD). This leads to dysfunctional assembling of the mitochondrial complex II at the inner mitochondrial membrane.

In most cases, sdhRCCs are low-grade tumors and associated with good prognosis of patients. Sarcomatoid features and high nuclear grade are predictive for metastatic spread of sdhRCCs.

Due to low case number and limited studies, there is currently no characteristic prognostic marker for sdhRCC.

MiT Family Translocation Renal Cell Carcinomas

Definition

MiT family translocation renal cell carcinomas are malignant tumors resulting from gene fusions involving members of the MiT family of transcription factors. The most common genetic alteration is Xp11 translocation, causing 40% of pediatric RCCs. t(6;11) translocation-associated RCCs are rare with approximately 50 published cases (Holger Moch et al. 2016).

Macroscopy

There are no macroscopic features characteristic for MiT family translocation RCCs (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

MiT family translocation RCCs often show a papillary growth pattern and are composed of epithelial clear cells with abundant psammoma bodies. However, Xp11 translocation RCCs might also appear as other renal neoplasms. Characteristics of t(6;11) translocation RCCs involve a biphasic pattern, composed of large epithelial cells growing in nests as well as smaller cells clustered around basement membranes (Holger Moch et al. 2016).

MiT family translocation renal cell carcinomas characteristically harbor gene fusions between two members of the MiT family of transcription factors. There are Xp11 translocation RCCs with gene fusions involving the transcription TFE3 and one of multiple identified genes, accounting for approximately 40% of pediatric but only 1.6–4% of adult RCCs. The most common translocations are t(X;1)(p11.2;q21), resulting in the fusion of TFE3 and PRCC, and t(X;17)(p11.2;q25) resulting in the fusion between TFE3 and ASPSCR1. Less common are t(6;11) translocation RCCs harboring a gene fusion between MALAT1, a gene encoding a long non-coding RNA, and TFEB, resulting in TFEB overexpression (Holger Moch et al. 2016).

MiT family translocation RCCs consistently express PAX8 and other renal tubular markers but lack or underexpress epithelial markers. High nuclear TFE3 immunoreactivity and a TFE3 break-apart FISH assay are highly specific and sensitive for the detection of Xp11 translocation RCCs. t(6;11) translocation RCCs consistently express melanoma markers such as melan A and HMB45 and the cysteine protease cathepsin K. Nuclear TFEB expression and translocation detection by FISH are highly specific for t(6;11) translocation RCCs (Holger Moch et al. 2016).

Independent predictive markers for RCC-associated death are distant metastases and older age at time point of diagnosis (Ellis et al. 2014). Different fusion subtypes go along with different tumor manifestation, for example, patients with ASPSCR1-TF3 fusion tumors develop more often lymph node metastases compared to patients harboring other gene fusions.

Renal Medullary Carcinoma

Definition

Renal medullary carcinoma (rmCA) is a rare RCC subtype with approximately 200 described cases, predominantly in Blacks and associated with sickle cell trait or other hemoglobinopathies. These highly aggressive tumors occur mostly in young adults and have metastasized at time point of diagnosis in the majority of cases (Holger Moch et al. 2016).

Macroscopy

rmCA is a solid tumor located centrally on the renal medulla, is poorly circumscribed, and has as grayish/white cut surface (Holger Moch et al. 2016).

Histopathology, Immunohistochemistry, and Molecular Pathology and Their Relevance for Prognosis

rmCA shares pathologic characteristics with collecting duct carcinoma and urothelial

carcinoma. Histological characteristics are features corresponding to high-grade adenocarcinoma histology including tubular, glandular, and tubulopapillary patterns with necrosis, inflammation, and desmoplasia. Tumor cells harbor prominent atypia and intracytoplasmic mucin. Stroma often appears myxoid in association with microabscesses and inflammatory infiltrates (Holger Moch et al. 2016).

Tumor cells consistently express PAX8; in about 50%, tumor cells are positive for polyclonal carcinoembryonic antigen, CK7, and CAM5.2. The stem cell marker Oct3/4 is expressed in the majority of renal medullary carcinoma and used as diagnostic marker (Rao et al. 2012).

Development of rmCA is associated with genetic alterations of hypoxia-inducible factor, p53, and vascular endothelial growth factor reflecting the underlying pathophysiological role of the hypoxic microenvironment of the renal medulla.

As rmCA is generally associated with poor survival of patients and account for less than 1% of all renal tumors, there are no independent prognostic markers routinely used to predict survival of patients.

Emerging New Tumor Entities

The 2013 ISUP Vancouver classification of renal neoplasia established a category of emerging new entities which include (Holger Moch et al. 2016):

- Thyroid-like follicular RCC
- Succinate dehydrogenase B mutation-associated RCC
- ALK rearrangement-associated RCC
- RCC MiT angioleiomyomatous stroma
- Oncocytic RCC occurring after neuroblastoma

To date, these emerging entities are not sufficiently characterized regarding morphology and molecular features. Additionally, due to rare case numbers and new definition of these subtypes, there are limited independent studies analyzing clinical course and outcome of patients. Thus, further studies are needed to characterize these new entities, to define diagnostic criteria and to increase knowledge about disease progression (Srigley et al. 2013). It remains uncertain if these tumors will be included as new entities in the WHO classification of tumors of the kidney.

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