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INVITED REVIEW

# Biomarkers in renal cancer

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**Abstract** Treatment options for primary and metastatic renal cancer are increasing. Accurate data from the pathological examination of renal cancer specimens aid clinicians in stratifying patients for surveillance and adjuvant therapies. This review focuses on biomarkers in diagnosis, prognosis and prediction of the biologic behavior of renal tumors which should be recorded in pathology reports and which are under investigation. Special emphasis is given to the use of immunohistochemical markers in differential diagnosis of various renal tumor subtypes. The relevance of cytogenetic and molecular findings is also discussed. The review includes the 2012 International Society for Urological Pathology Consensus conference recommendations.

**Keywords** RCC · Staging · Grading · Immunohistochemistry · Biomarker · Molecular pathology

## Introduction

Biomarkers in renal cell carcinoma (RCC) are of help in pathological diagnosis, classifying new entities, and include predictive and prognostic markers. Immunohistochemistry allows the characterization of renal tumor subtypes, whereas novel molecular analyses are mainly used to characterize specific molecular pathways involved in different tumor subtypes. They are also useful to identify potential therapeutic targets. This article will review the key prognostic factors with an emphasis on the use of immunohistochemical markers in routine practice. The review is intended to complement the International Society of Urological Pathology (ISUP) conference on renal cancer held in Vancouver in 2012 [1, 2].

## Old and new subtypes of renal cell neoplasms

In adults, the main morphotype of RCC, when correctly classified, is the strongest prognostic biomarker in addition to tumor stage and grade [3, 4]. The current World Health Organization Classification of Renal Tumors was established 2004 [5]. In adults, the main subtypes are clear cell, papillary, chromophobe, collecting duct, and unclassified RCC, but various other subtypes have been recognized in the 2004 WHO classification, including mixed epithelial and stromal tumors (MEST), mucinous tubular and spindle-cell carcinoma (MTSC), and translocation cancer. Oncocytoma, angiomyolipoma, and metanephric adenoma are considered benign renal neoplasms. At the ISUP conference, a consensus was reached to recognize five entities as new distinct epithelial tumors: tubulocystic RCC, acquired cystic disease-associated

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RCC, clear cell (tubulo) papillary RCC, the MiT family translocation RCCs (including t(6;11) RCC), and hereditary leiomyomatosis RCC syndrome-associated RCC. Thyroid-like follicular RCC, succinate dehydrogenase B deficiency-associated RCC and ALK translocation RCC were regarded as emerging new entities (Figs. 1, 2 and 3) [1]. Subtyping of papillary RCC (types 1 and 2) provides additional prognostic information. For the time being, the oncocytic variant of papillary RCC is not considered as a distinct entity. Clear cell (tubulo)papillary RCC is associated with a more favorable outcome. Multicystic clear cell RCC is considered as a neoplasm of low malignant potential within the group of clear cell RCC. The hybrid oncocytic chromophobe tumor occurs in Birt-Hogg-Dubé Syndrome, in renal oncocytosis and also as a sporadic neoplasm. Hybrid oncocytic chromophobe tumors are indolent tumors grouped, at least for the time being, in the chromophobe RCC category. Epithelioid angiomyolipoma is nowadays considered a potentially malignant variant of angiomyolipoma, because metastatic disease has been reported in some patients with this specific subtype of angiomyolipoma. Cystic nephroma and mixed epithelial and stromal tumor are seen as a morphological spectrum within a single tumor type [1].

#### Perinephric fat invasion as a staging parameter

The 2009 TNM system has minor changes compared to the 2002 TNM system, notably in clarifying that infiltration of renal sinus (peripelvic) fat is part of perinephric tissue involvement in the pT3 tumor category [6, 7]. Perinephric fat invasion is prognostically relevant, as it is associated with a significant decrease in 5-year overall survival [8]. Perinephric fat invasion was defined at the 2012 ISUP conference as either the tumor touching the fat or extending with irregular tongues into the perinephric tissue, with or without desmoplasia [9]. Importantly, recent studies have shown the relevance of renal

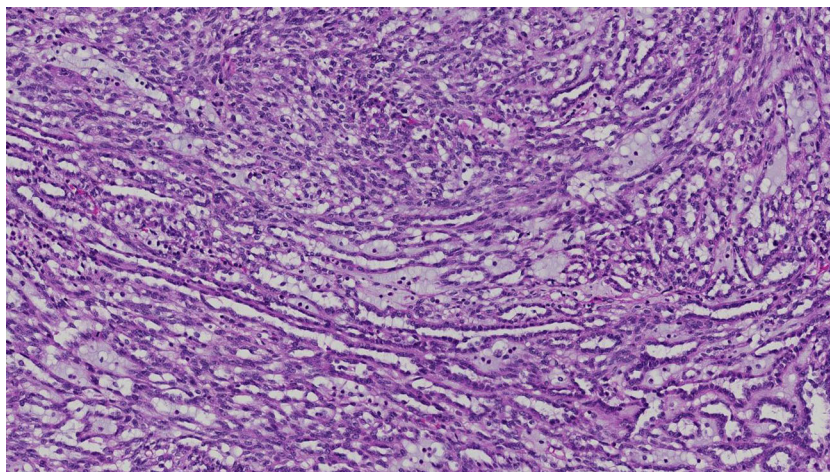
sinus invasion in renal cancer [10, 11]. The frequent renal sinus invasion in early-stage tumors has been overlooked for many years, but has significant prognostic implications. Renal sinus invasion is present when the tumor is in direct contact with the fatty tissue or the loose connective tissue of the sinus. Involvement of any endothelial lined spaces within the renal sinus is considered as renal sinus invasion, regardless of the size of the vascular space [9].

#### Tumor grade, sarcomatoid differentiation, and necrosis as prognostic biomarkers of renal cancer

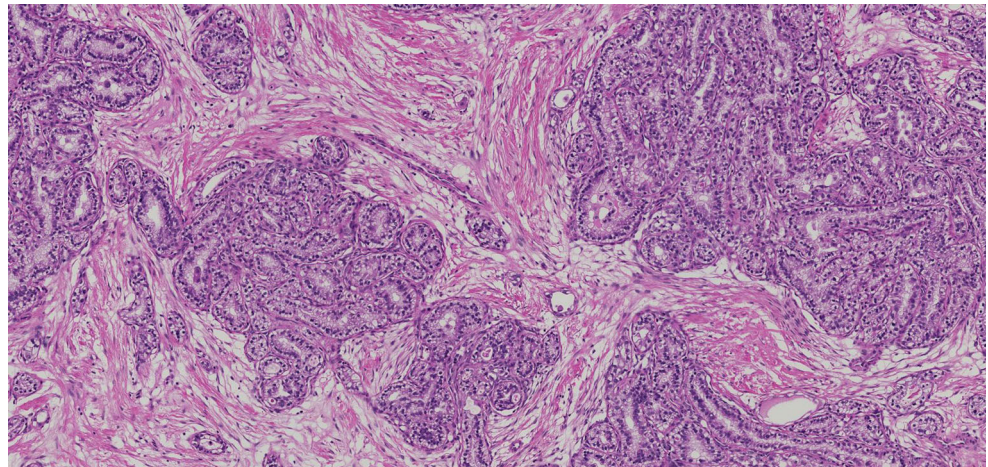
The Fuhrman grading system has been in use for over 30 years and is still the most widely utilized grading system for renal cancer [12]. Nonetheless, it has not evolved over the years to accommodate our increasing understanding of the nature and biological spectrum of renal carcinoma. Furthermore, its use has become controversial, as it is increasingly recognized that its application is not without problems [13, 14]. In addition, the grading system has not been validated for many of the morphotypes of renal cell carcinoma. In view of the problems associated with the application of Fuhrman grading, a new grading system was endorsed at the recent ISUP consensus conference [3]. Nucleolar prominence defines grades 1 to 3 of clear cell and papillary RCCs, whereas extreme nuclear pleomorphism or sarcomatoid and/or rhabdoid differentiation defines grade 4 tumors. The ISUP grading system was endorsed as a prognostic parameter for clear cell renal cell carcinoma. In addition, a consensus was reached that chromophobe RCC should not be graded [15–17], as irregular nuclei, prominent nucleoli, and nuclear pleomorphism are inherently present in chromophobe RCC, even in cases with good prognosis [3].

Different grading systems for chromophobe RCC have been proposed [15], but these were not endorsed at the 2012 ISUP consensus conference. Sarcomatoid and/or rhabdoid differentiation and tumor necrosis were accepted as useful

**Fig. 1** Mucinous tubular and spindle-cell carcinoma showing classical pattern with elongated tubules, spindle-cell areas, and stromal mucin

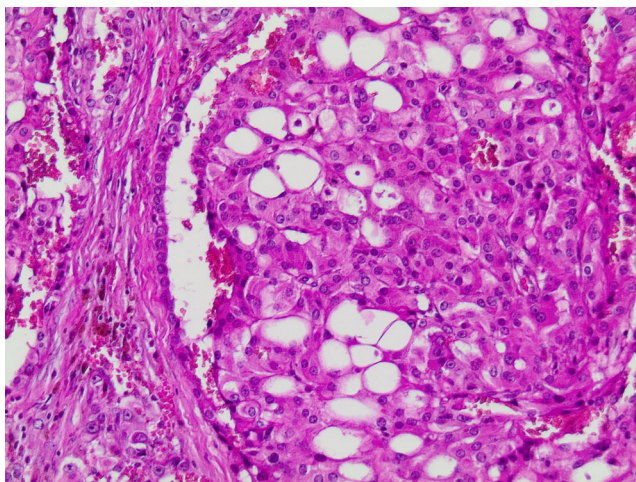


**Fig. 2** New tumor entity: leiomyomatous renal cell carcinoma. Note nests and tubules lined by clear cells embedded in smooth muscle



additional histopathologic prognostic parameters [4]. Sarcomatoid or rhabdoid differentiation should be mentioned in pathology reports of all RCC subtypes. For a correct tumor classification, the underlying carcinoma subtype should be reported, because this can be recognized for all main subtypes. If the underlying carcinoma subtype cannot be recognized in sarcomatoid RCC, the tumor should be classified as a grade 4 unclassified carcinoma with a sarcomatoid component. Tumor necrosis is considered of prognostic significance and the amount of necrosis should be quantified in clear cell RCC. In contrast, intratumoral microvascular invasion should not be included as a staging criterion for RCC [4, 9].

RCC is considered to be susceptible to the innate and adaptive immune responses of the host because a small subset of patients with advanced disease achieves spontaneous or immunotherapy-induced complete remission. The cellular and molecular mechanisms underlying these complete remissions are not completely understood, although a variety of inflammatory cells including T and Natural killer (NK) cells



**Fig. 3** New tumor entity: Renal cell carcinoma in end-stage renal disease. Note cytoplasmic vacuolation

have been identified in RCC lesions. Local immunoregulatory processes may have an impact on disease progression and therefore on survival of patients with primary clear cell renal cell carcinoma. Earlier data have shown that a high number of tumor-infiltrating lymphocytes and/or macrophages are associated with poor prognosis [18–20].

#### Differential diagnosis of renal cell neoplasms using immunohistochemical biomarkers

Most renal cancer subtypes have a characteristic immunohistochemical staining profile that helps in the correct tumor classification. It has been shown that upregulation of CD10 and Pax 2 expression is due to VHL inactivation in clear cell RCC [21, 22], while CAIX is also consistently expressed due to its regulation by the VHL protein [23, 24]. Papillary RCC type 1 stains for vimentin, broad spectrum keratins, CK7, AMACR and RCC marker, but not for CD117, kidney-specific cadherin, and parvalbumin. Papillary RCC type 2 has variable staining patterns. Whereas papillary type 1 RCC frequently show diffuse CK7 immunoreactivity, papillary type 2 RCC are less often positive for CK7, in a staining pattern comparable to that of clear cell RCC with only focal CK7 expression. Chromophobe RCC are negative for vimentin (Table 1), but show diffuse reactivity for E-cadherin, kidney-specific cadherin, parvalbumin, CD117, EMA, broad spectrum keratins, and CK7 [1, 4]. To differentiate between benign oncocytoma and chromophobe RCC, specifically its eosinophilic variant, is difficult as these tumors have overlapping histological and immunohistochemical characteristics. CK7 is the best marker to differentiate between these two tumor entities. Most chromophobe RCCs show membranous CK7 expression in tumor cell clusters or in the majority of tumor cells while oncocytoma is typically negative or at most focally positive in scattered cells [25, 26]. Other biomarkers useful for this differential diagnosis are summarized in Table 2.

**Table 1** Biomarkers in clear cell and chromophobe RCC

Biomarker	Clear cell RCC	Chromophobe RCC
CK7	– (focal)	+
RCC marker	+	–
CD10	+	–
Vimentin	+	–
CD117	–	+
Parvalbumin	–	+
E-cadherin	–	+
EMA	+	+
MUC1	+	+
CK20	–	–
AMACR	–	–

Collecting duct carcinomas often show immunoreactivity for EMA, CK7, high molecular weight keratin, Pax 2 and/or Pax 8 [27] (Table 3). Pax 2 and/or Pax 8 are frequently expressed in different renal carcinoma subtypes and represent useful markers in the differential diagnosis of a primary renal carcinoma, although expression patterns need to be interpreted in conjunction with other markers. For instance, expression of Pax 8 has been reported in primary pancreatic neuroendocrine tumors, which can mimic metastatic RCC [28]. Distinction from RCC will therefore require additional support, including the lack of expression of neuroendocrine markers for a diagnosis of RCC. There is consensus that TFE3 and TFEB immunostains should be requested in order to diagnose RCC in a young patient or when histological appearances are suggestive of the translocation subtype of RCC [4].

Epithelioid angiomyolipoma closely resembles RCC [3, 29]. Positive immunoreactivity for HMB45, melan-A and SMA, and absence of expression of keratins, helps in the diagnosis of angiomyolipoma [30]. Metanephric adenoma can be mistaken for type 1 papillary RCC. The former shows positive immunostaining for WT1, CD57, and absence of

**Table 2** Biomarker in chromophobe RCC and oncocytoma

Biomarker	Chromophobe RCC	Oncocytoma
CK7	+	–/focal +
MOC31	+	–
EpCam	+	–
Caveolin-1	+	–
EABA	–	+
CD82	+	–
S100A1	–	+
Parvalbumin	+	+
Ksp cadherin	+	+
CD117	+	+

**Table 3** Biomarker for poorly differentiated carcinomas

Antibody	RCC, unclassified	Collecting duct carcinoma	Urothelial carcinoma
CK7	–/+	+	+
CK20	–	– (rarely focal+)	+/-
P63	–	– (rarely+)	+
RCC	+/-	–	–
Vimentin	+/-	+	–/+
CD10	+/-	–	–/+
CK5/6	–	–	+/-
INI1	+	+	+
Ulex-1	–	+	–/+
PAX8	+/-	+	–/rarely +
PAX2	+/-	+/-	–
GATA3	–/(rarely focal +)	–	+

reactivity for AMACR [31]. AMACR, CK7, WT1, and CD57 are therefore useful to distinguish metanephric adenoma from papillary RCC (Table 4).

### Molecular prognostic biomarkers

Biomarkers for potential prognostication of RCC include molecules in intracellular pathways and/or specific DNA alterations. Most of them have not entered clinical practice. Clear cell RCC is characterized by loss of chromosome 3p and mutations of the von Hippel Lindau (*VHL*) gene [32]. *VHL* mutations have been reported in the majority of sporadic clear cell renal carcinomas [33]. These mutations can impact on the hypoxia inducible factor (HIF) pathway and their existence provides the theoretical molecular explanation for the success of HIF targeted treatment strategies in some patients with clear cell RCC (see below) [34, 35]. Dysregulation of HIF leads to upregulation of the expression of downstream molecules, including Carbonic anhydrase 9 (CAIX). One study found an association between CAIX expression and grade of clear cell RCC [36]. Diminished CAIX expression was independently correlated with poor survival in advanced renal cell cancer patients [37]. Some other chromosomal abnormalities may have prognostic value, such as loss of chromosome 9p in clear cell RCC, which is associated with a significantly poorer cancer specific survival [38, 39].

A relatively new finding is the frequent polybromo-1 (*PBRM1*) and *BAP 1* mutation on chromosome 3p in a surprisingly high percentage of clear cell RCC [40]. Loss of *PBRM1* protein expression product BAF180 was shown to be associated with advanced tumor stage and worse patient outcome [41]. All of these newly identified mutations target

**Table 4** Biomarker for renal tumors with papillary or tubulopapillary architecture

Antibody	Papillary RCC	Collecting duct carcinoma	Metanephric adenoma	Mucinous tubular and spindle-cell carcinoma	Clear cell papillary RCC
CK7	+	+	– (only focal)	+	+ (diffuse)
CD10	+	–	–	–/+	–
RCC	+	–	–	variable	–/+
AMACR	+	–	–/+	+	–
EMA/MUC1	+	+	– (may be focal)	+	+
WT1	–	–	+	–	–
CD57	–	No data	+	–	No data
Ulex-1	–	+	–	–	No data

genes which are responsible for chromatin remodeling. Future studies will help to understand the tumor suppressor gene network between *VHL* and the other genes on chromosome 3p. Compared to other solid tumors, intratumoral heterogeneity of driver gene mutations is very pronounced within primary RCC as well as between primary tumors and their metastases [42, 43]. The process of clonal evolution of renal cancer cells is very complex, and this has potential consequences for tumor progression, development of resistance against targeted therapies, with clinical impact.

Papillary RCC is characterized by numerical abnormalities, often trisomies of chromosomes 7 and 17 [44]. Chromophobe RCCs harbor multiple numerical losses of chromosomes 1, 2, 6, 10, and 17 [45]. Translocation RCCs are defined by translocations involving chromosome Xp11.2, resulting in *TFE3* gene fusions [46]. Another variant of translocation associated RCC is characterized by fusion of the *TFEB* gene on chromosome 6p with the *alpha* gene on 11q12, which leads to expression of the *TFEB* protein [47, 48].

Cytogenetics and novel molecular technologies are rarely used in renal carcinoma diagnosis, but have contributed to tumor classification, understanding the histogenesis and the genotype/phenotype correlation in RCC. Some groups recommend a panel of fluorescence in situ hybridization (FISH) probes for the differential diagnosis of RCC. For instance, numerical abnormalities of chromosomes 7 and 17 on FISH favor a diagnosis of papillary RCCs over clear cell RCC. The value of FISH in diagnosing a translocation RCC with equivocal immunohistochemical results has recently been emphasized [49].

### Predictive markers in renal cancer

Predictive markers provide information on whether a particular cancer will respond to or be resistant to a specific type of therapy. In contrast to other solid tumors, e.g., lung and colorectal cancer or melanoma, use of predictive biomarkers

for clinical stratification and management planning has not yet entered routine practice in metastatic renal cancer [4, 50, 51]. In 2007, six new agents, which target complex molecular pathways regulating tumor angiogenesis and cell proliferation and survival, have been approved. These treatments have significantly improved survival times in metastatic renal cell carcinoma [52]. Patients with advanced clear cell RCC receive VEGF pathway antagonists, e.g., sunitinib or pazopanib. Analysis of *VHL* mutation status, plasma CAIX, VEGF, sVEGFR2, tissue inhibitor of metalloproteinase 1 (TIMP-1), and *Rasp21* has been performed in the TARGET trial comparing sorafenib with placebo in advanced RCC [53]. No predictive markers were identified [54, 55]. Choueiri and colleagues evaluated tumor CAIX expression using immunohistochemistry in patients treated with antiangiogenic therapies [56]. While CAIX expression was neither prognostic nor predictive of response to sunitinib, for sorafenib-treated patients, high CAIX expression (>85 %) was associated with decreased tumor size in response to treatment.

MicroRNAs (miRNAs, miRs) are small (19–25 nucleotides), non-coding RNAs that play an important role in apoptosis, survival, proliferation, and differentiation processes, by the post-transcriptional regulation of gene-expression. An increasing body of evidence suggests that micro RNA's play a crucial role, not only as oncogenic or tumor-suppressive molecules in cancer initiation, progression and metastasis, but also in resistance to chemotherapy or other systemic therapies. Therefore, miRNA's might constitute potential prognostic and/or predictive biomarkers. Prognostic miRNA expression patterns have recently been identified in RCC tissues [57, 58]. High levels of miR-210 were noticed in chemotherapy resistant ccRCC patients [59]. Downregulation of miR-141 was correlated with lack of response to sunitinib treatment in ccRCC patients, when compared to the expression profile in responding patients [60]. Gamez-Pazo and other groups provided evidence that the response of metastatic ccRCC patients to TKI inhibitors is correlated with a miRNA profile in patient serum [61–63].

## Conclusion

Correct tumor classification, histologic grading and systematic examination of radical nephrectomy or tumorectomy specimen are essential for patient management. Tumor stage, tumor type, and tumor grade are robust and independent histopathological prognostic factors, which should be routinely included in pathology reports. Evidence for other prognostic biomarker is lacking. In contrast to other cancers, e.g., lung and colorectal carcinomas or melanoma there are at present no predictive molecular biomarker, suitable for routine use. Future investigation of recently identified novel molecular alterations and tumor suppressor networks in clear cell RCC will help to clarify the biological relevance of different molecular signaling pathways in predicting therapy response.

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