Papillary renal cell carcinoma: current and controversial issues

Silvia Angori[a,*], João Lobo[b,c,d,*] and Holger Moch[a,e]

Purpose of review
Papillary renal cell carcinoma (pRCC) is the second most frequent renal cancer subtype and represents 15–20% of all RCC. Classification of pRCC is changing because novel tumour entities have been discovered in the last years. In this review, we summarise recent studies relevant for the understanding of the molecular complexity and the broader differential diagnosis of pRCC.

Recent findings
It has been 25 years ago, that pRCC was morphologically subdivided into type 1 and type 2. Recently described tumour entities in the 2022 WHO classification challenged this concept and allow a new view on the molecular background in pRCC. Biphasic hyalinizing psammomatous RCC and papillary renal neoplasm with reversed polarity are emerging tumour entities derived from the new concept of molecularly defined RCC subtypes. Immune checkpoint inhibition and tyrosine kinase inhibitors have been introduced as the new backbone in the first-line treatment of advanced pRCCs. To identify novel targeted treatments for patients with pRCC it is crucial to investigate the specific molecular background of pRCC considering emerging pRCC subtypes.

Summary
In the future, a deeper understanding of the correlation between molecular aberrations and new pRCC subtypes may improve the classification of pRCC patients and could reveal potential predictive biomarkers for each subgroup.

Keywords
emerging entities, histopathology, molecular pathology, papillary renal cell carcinoma, renal tumours

INTRODUCTION – EPIDEMIOLOGY, AND HISTOPATHOLOGY OF PAPILLARY RENAL CANCER

Although renal cell carcinoma (RCC) represents only 2% of cancer diagnoses and deaths, its incidence has more than duplicated in developed regions in the past decades [1] with more than 76,000 new cases and 14,000 deaths recorded in 2020 in the United States [2]. Incidence and mortality rates are higher in developed countries due to the presence of modifiable environmental exposures like smoking and diet, in addition to the contribution of nonmodifiable factors like male gender and ethnicity [3,4]. Survival is highly dependent on disease stage, being higher (>90%) in the overall 65% of patients presenting with localised disease, many diagnosed incidentally on imaging [4]. However, a clinically relevant proportion of patients (16%) are diagnosed with distant metastatic disease, which has a dismal prognosis (13.9% 5-year relative survival). There is an unmet need of novel targeted therapies for these metastatic patients, especially since RCC is generally chemo- and radio-resistant [5].

The biggest challenge to this has been the tremendous heterogeneity of renal cancers [6]. RCCs are grouped on several categories by the most recent

[a]Department of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland, [b]Department of Pathology, Portuguese Oncology Institute of Porto (IPOP), [c]Cancer Biology and Epigenetics Group, IPO Porto Research Center (GEBC CI-IPOP), Portuguese Oncology Institute of Porto (IPO Porto) & Porto Comprehensive Cancer Center (P.CCC), R. Dr António Bernardino de Almeida, [d]Department of Pathology and Molecular Immunology, ICBAS−School of Medicine and Biomedical Sciences, University of Porto (ICBAS-UP), Porto, Portugal and [e]Faculty of Medicine, University of Zurich, Zurich, Switzerland

Correspondence to Holger Moch, MD, Department of Pathology and Molecular Pathology, University Hospital Zurich, Schmelzbergstrasse 12, CH 8091 Zurich, Switzerland. Tel: +41 44 255 25 00; e-mail: holger.moch@usz.ch

*Silvia Angori and João Lobo are joint first authors.

KEY POINTS

- pRCC was subdivided in type 1 and type 2 according to the morphology but the recent identification of new tumour entities highlights the need of a deeper understanding of the molecular background of this tumour type.

- Targeted treatments for pRCC are limited and response rate of these patients to new therapies is usually quite low.

- Comprehensive characterisation of the genetic background of pRCCs identifies large chromosomal number changes and several mutated genes as MET, CDKN2A, SETD2, BAP1, PBRM1, NFE2L2 and mTOR as characteristic tumour features.

- The correlation of different morphologies with genomic analysis will allow for a better classification of pRCC patients and for the design of targeted and personalised treatment strategies.

World Health Organization (WHO) Classification [7] (which will be updated in 2022). Around 75% of RCCs correspond to clear cell RCCs (ccRCCs), which have been the most studied in the field of biomarkers and targeted therapies, leaving nonccRCC patients with less treatment options [8].

Papillary RCC (pRCC) comprises the second most frequent RCC subtype (10–15% of RCCs). Although advocated to have a better prognosis in direct comparison to ccRCC in organ-confined stage, it is reported that pRCC histology in disseminated disease displays poorer outcomes compared to ccRCC [9]. pRCC is, however, a very heterogeneous disease. The first attempt to subclassify pRCC based on morphology was proposed in 1997 by Delahunt and Eble, who divided tumours in type 1 pRCC (slender papillae, with a single layer of small basophilic or amphophilic cuboidal cells lining them) and type 2 pRCC (broader papillae, filled with several layers of large eosinophilic cells, with nuclear pseudostratification and larger nucleoli) [10]. This was later supported by molecular data and adopted by the WHO classification [11], and corroborated by large studies, such as The Cancer Genome Atlas (TCGA) analyses [12–14]. Although some clinical studies suggest type 2 pRCC to have higher nuclear grade and other histopathological features of aggressiveness [15,16], this did not translate to worse patient outcome when adjusted for stage and other variables [17,18]. Moreover, it is now recognised that mixtures of type 1 and 2 areas frequently coexist [19], and it is possible that these represent a progression of low to high tumour grade [20■]. Finally, the spectrum of pRCC (particularly of type 2 pRCC) has suffered several modifications over the past years [20■].

THE SPECTRUM OF RENAL CANCER SUBTYPES WITH PAPILLARY GROWTH – RECENT AND EMERGING ENTITIES

Various works revisiting series of RCCs with papillary features and studying their molecular and clinical background allowed for discrimination of new tumour entities [21■■,22■,23,24], already incorporated in the WHO classification (e.g. tubulocystic RCC [25], clear cell papillary RCC [26], fumarate-hydratase deficient RCC [27] and TFE3 or *TFEB*-translocated RCC [28]). Additionally, some emerging entities have been proposed [29,30], for which more data is currently being gathered, further purifying the true pRCC family of tumours and decreasing the proportion of cases diagnosed as 'unclassified RCC' [31,32].

Further, current evidence does not support the discrimination of so-called 'oncocytic pRCC' as an independent entity, since oncocytic change maybe be observed in otherwise typical type 1 or 2 pRCC [33] or in papillary renal neoplasm with reversed polarity (see below). Indeed, a subset of cancers previously considered as type 2 or 'oncocytic pRCC' are now known to correspond to fumarate hydratase-deficient RCCs [34]. Although their morphology can be quite variable, some features can suggest the diagnosis, such as the large reddish inclusion-like nucleoli surrounded by a clear halo [35]. The distinction is important since these are aggressive cancers, with frequent dissemination, and can point to the discovery of a yet undiagnosed hereditary and leiomyomatosis and renal-cell cancer syndrome (HLRCC) syndrome due to germline mutations in *FH* [36], which can also have implications for treatment [37,38].

Other tumour entities which could have been considered in past series in the pRCC family of tumours include MiT translocated RCCs, both *TFE3*-translocated RCC (Xp11 translocation) and *TFEB*-translocated RCC (t(6;11)) [39]. The variety of architectural patterns mixed together within one tumour, with papillary, nested and tubular growth and presence of clear and eosinophilic cells (biphasic appearance) can suggest the diagnosis [40], which is confirmed by fluorescence *in situ* hybridisation (FISH) [41,42]. More recently, *TFEB*-amplified RCCs were also described, which have high-grade cytological features and aggressive behaviour [22■,43]. *ALK*-translocated RCC has also been reported and considered as a very rare RCC subtype [44]. It has the widest range of morphologies described, including papillary features. Its discrimination from pRCC or nonclassified RCC by

FISH testing is relevant since current *ALK* inhibitors have demonstrated clinical efficacy [45,46].

Our knowledge on the morphology and molecular background of pRCC has continued to evolve, and currently a set of emerging entities is proposed. Although their prevalence is overall low [20■], continuing studying and accumulating evidence on these entities may contribute to better assessment of patients' prognosis and treatment decisions.

Biphasic squamous-alveolar RCC, the most frequent of these entities [20■], shows a phenotype closer to type 1 pRCC. The tumour is composed of two cell populations, one of large eosinophilic cells, with higher nuclear grade and squamoid features clustered together in nests and surrounded by a second population of smaller cells, with lower nuclear grade, giving the lower-power impression of multiple alveolar/organoid structures [47]. The large cell population is evidenced by specifically staining for cyclinD1 and CD57 [48,49]. Emperipolesis is another characteristic feature, seen in all cases of a large series [50], considered by others to be more precisely cytophagocytosis of neutrophils [51]. Frequent transition to otherwise classical papillary areas, different proportions of the alveolar pattern between tumours and the typical gains of chromosomes 7/17 in all cases support that these tumours are within the pRCC (type 1) morphological spectrum [50,52]. Data supports that *MET* is a major driver of these RCCs in particular, and the high frequency of *MET* mutation should trigger investigations of therapy with *MET* inhibitors [53].

Biphasic hyalinizing psammomatous RCC is another emerging entity with evident papillary/tubulo-papillary architecture. It also shows admixture of two cell populations, one of small cells, sometimes spindle-shaped, arranged predominantly around basement membrane material, giving the impression of pseudo-rosettes (a feature also observed in *TFEB*-translocated RCC) or forming branching nodules or clusters within larger acini and tubules which are formed by larger eosinophilic cells. The mixture of the two gives the low-power impression of a glomerular pattern [54]. The stroma is sclerotic and frequently shows psammoma bodies. Although EMA stains preferentially the small cells, CK7 stains predominantly the large cell population. This tumour phenotype is associated with somatic *NF2* mutations. This entity was recently described in a single study of eight patients (one of which died from disease), and therefore needs additional work to clarify about its clinical relevance and biology, namely if such *NF2* mutations are the true driver genetic abnormalities. Recently, *NF2* gene inactivation was described in a cohort of advanced stage pRCC, which could have implications for risk stratification [55] and for targeted therapies, as mentioned above.

Another recently described emerging entity is papillary renal neoplasm with reversed polarity [56]. Tumours are usually small and can be partly cystic [57]. They have a quite characteristic morphology, recapitulated in several recent publications [56,58–63], composed of thin papillae with hyalinised cores filled with a single row of eosinophilic cells with small uniform nuclei (sometimes with optical clearing) aligned and pushed against the apical pole (reversed polarity), frequently with peritumoral lymphoid aggregation. In the past, they have probably been fit into a 'low-grade oncocytic pRCC' designation, due to their low-grade cytology and absence of aggressive features, in line with their good clinical behaviour [61]. Although classical gains of chromosomes 7 and 17 are found, GATA3 and L1CAM nuclear positivity and *KRAS* mutations are particular findings that can aid in diagnosis.

Additional emerging entities/disease phenotypes which need further investigation include Warthin-like pRCC [64], a papillary tumour with eosinophilic papillae and with stroma filled by brisk lymphocytic infiltrate, resembling Warthin tumour of the parotid gland, and also thyroid-like follicular RCC [65,66], which resembles thyroid follicular architecture, with cuboidal cells around colloid material, possibly having papillary foci [67]. The latter has recently been reported to harbour *EWSR1-PATZ1* fusions and also to possibly have aggressive behaviour [68–70], and more studies are required to fully understand the clinical relevance of this phenotype. Illustrative photomicrographs of emerging entities are presented in Fig. 1.

MOLECULAR BACKGROUND OF PAPILLARY RENAL CANCER – RECENT DEVELOPMENTS AND TREATMENT OPPORTUNITIES OF METASTATIC PAPILLARY RENAL CELL CARCINOMA

The novelties in classification together with a deeper investigation of the molecular background of pRCCs may also open the way for specific targeted therapies for these patients. Among different molecular features, large somatic copy number changes of pRCC have been reported decades ago by G. Kovacs *et al.* [71,72,73■]. Chromosome 7 and 17 gains are nearly universally seen in type 1 pRCC, whereas type 2 pRCC is more characterised by gains in chromosomes 12, 16 and 20. Other chromosomal gains are also described for chromosome 2 and 3 [72,74,75]. Interestingly, TCGA identifies three subgroups of pRCC with different copy number alteration pattern. Low-grade tumours compose one
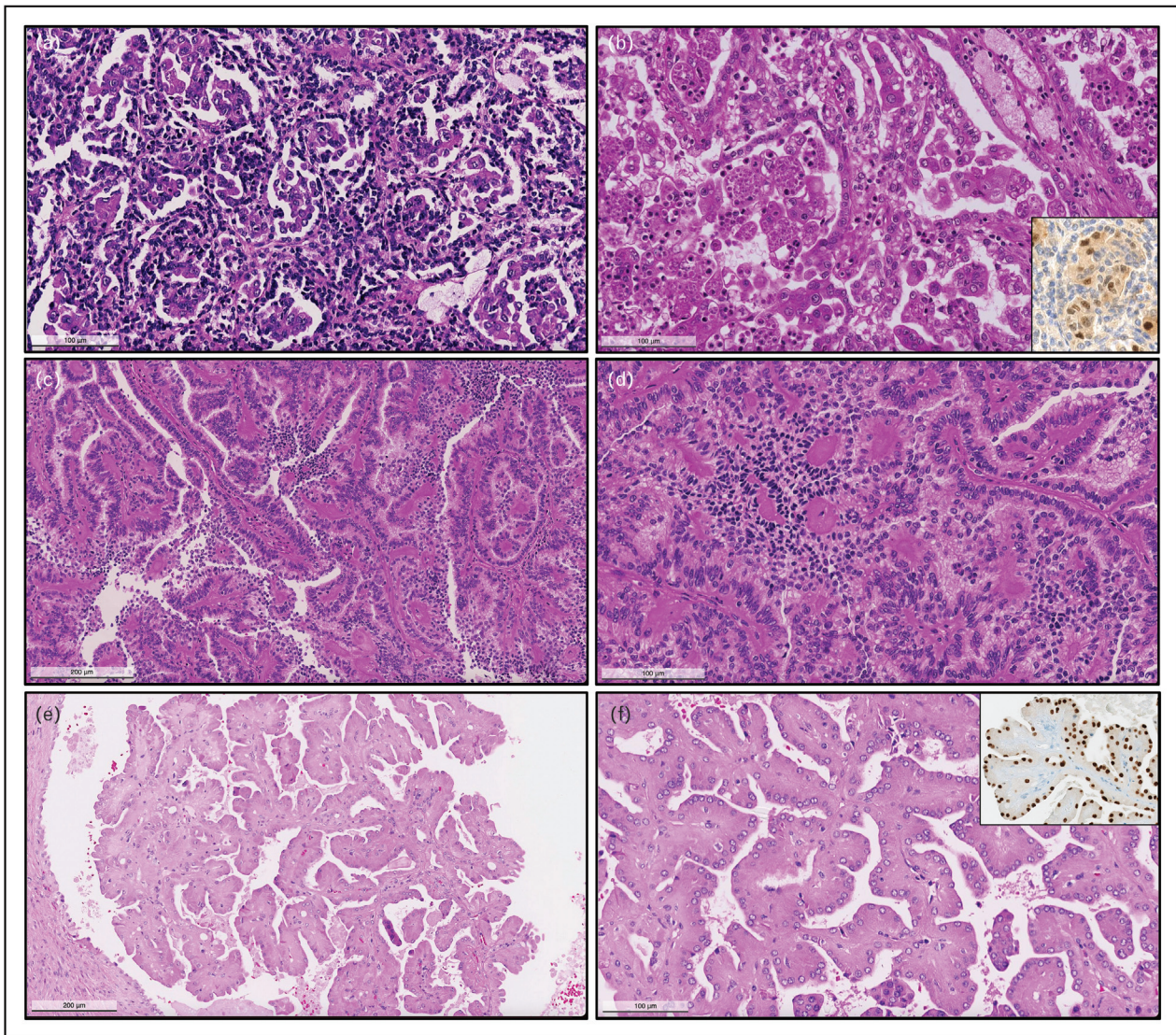
FIGURE 1. Histopathological features of emerging entities within the spectrum of papillary renal cell cancer. a,b: Biphasic squamous-alveolar renal cell carcinoma. The tumour is composed of two cell populations, one of smaller cells with low nuclear grade surrounding a second population of larger eosinophilic cells, with higher nuclear grade, forming alveolar structures (a). The larger cells have squamoid cytoplasmic features, and frequently phagocyte neutrophils. Scattered foamy histiocytes typically found in papillary renal cell carcinomas are seen (b). The large cells staining for cyclinD1 (inset). c,d: Biphasic hyalinizing psammomatous renal cell carcinoma. The tumour is also composed of two cell populations, one of small cells with dark nuclei, sometimes spindle-shaped, and other of larger cells lining papillae (c). The small cells tend to surround strongly eosinophilic basement membrane material, forming pseudo-rosettes (d). e,f: Papillary renal neoplasm with reversed polarity. The tumour is small, and is formed within a cystic space (e). The papillae are hyalinized and tumour cells are strongly eosinophilic. The nuclei are small, low grade, show optical clearing and are pushed against the apical pole of the cells (f). The nuclei stain with GATA3 (inset).

subgroup predominantly with gain of chromosomes 7, 12, 16, 17 and 20. The other two subgroups behave completely differently. Although one group shows only few alterations, the other one is characterised by high genome instability and loss of chromosome 9p associated with poor survival [14,76]. In few cases, intra-chromosomal rearrangements of chromosomes 1, 2 and 3 are also described [72].

Recently, several genes have been found to be mutated in pRCC. Germline or somatic mutations in the proto-oncogene *MET* are found mainly in type 1 pRCC. Mutations or promoter hypermethylation of *CDKN2A* are strongly associated with aggressive pRCC. Loss of *CDKN2A*, encoding for p16, results in increased expression of cell-cycle related genes [77]. In addition, mutations in

chromosome modifier genes *SETD2, BAP1,* and *PBRM1* are also described in pRCC. Although these genes, commonly mutated also in ccRCC, are associated with loss of chromosome 3, no chromosomal change is usually observed in pRCC tumours. Other common mutated genes are *FAT1, FLCN, TERT, NF2, NFE2L2, STAG2* and *TP53*, which are involved in chromatin modification, cell cycle and metabolism [14,78,79]. Numerous mutated genes in pRCC are components of well-described cancer pathways like Hippo, mTOR or p53 [14]. The Hippo pathway controls cell proliferation by inhibiting the transcriptional co-activator protein YAP1. In pRCC, loss of NF2 leads to over-activation of YAP1 and, consequently, to abnormal cellular growth [80,81].

Aberrations in genes as *mTOR, PIK3CA, PTEN* or *FBXW7, RB1,* and *TP53* state the involvement of mTOR and p53 pathways in pRCC. These two pathways are crucial for cell division and proliferation, apoptosis and response to stress [82,83]. In cancer cells, aberrations in these pathways can contribute to tumorigenesis and progression of RCCs [84–86]. Mutations in *TP53* correlate, indeed, with poor patient survival [87]. Lastly, mRNA enrichment analysis on TCGA data shows over-activation of the Nrf2-ARE pathway in aggressive pRCCs [14]. Mutations in key genes of this pathway such as *NFE2L2, CUL3* or *Keap1* lead to the constitutive activation of Nrf2, a transcription factor responsible for cell proliferation under oxidative stress conditions [88,89].

Over-expression of the Cerebellar degeneration-related protein 2 (Cdr2) was also described as a potential biomarker in pRCC due to the reduction of HIF response under hypoxia [90].

FH is often mutated in the aggressive HLRCC [14], which represents an own and independent tumour subtype. Since *FH* mutations are also seen in sporadic tumours, this tumour entity will be renamed into *FH*-deficient RCC in the up-coming WHO classification.

A summary of treatment options for advanced/metastatic pRCC patients is presented in Table 1. Targeted treatments for pRCC are limited and new therapies have not significantly improved patient survival [91]. However, the heterogeneous molecular background of pRCC tumour should be taken into consideration for personalised targeted strategies. For example, pRCC shows recurrent alteration in *MET* by gene amplification or mutations. MET is a tyrosine kinase transmembrane receptor that binds the Hepatocyte Growth Factor (HGF) to regulate cell growth, proliferation and angiogenesis. Aberrant activation of MET leads to tumorigenesis, metastases migration and invasiveness [92]. Given the frequent MET over-expression in pRCC, several inhibitors have been used in the treatment of these patients. Cabozantinib, a dual MET-VEGF inhibitor, was approved in 2016 for the treatment of pRCC patients and it became a broad treatment for all nonccRCCs [91,93]. Recent studies showed that Savolinib, a potent and selective MET kinase inhibitor, has higher efficacy compared to Sunitinib in the treatment of tumours with MET alterations [94,95■■]. MET activation is also often associated with the Epidermal Growth Factor Receptor (EGFR) expression in pRCC. Therefore, combination of MET and EGFR inhibitors (Tivantinib and Erlotinib [96–98]) can represent a treatment strategy in MET-driven pRCC tumours [97,99].

According to the latest ESMO guidelines, systematic treatments of advanced or metastatic nonccRCC patients include immune checkpoint inhibitors (ICIs) such as anti-PD1/PDL1 antibodies and tyrosine kinase inhibitors (TKIs) [95■■]. Although PD1-PDL1 inhibitors can restore the T-cell response against tumour cells [100–102], TKIs are able to target the downstream targets of the VHL pathway such as vascular endothelial growth factor (VEGF) or platelet-derived growth factor (PDGF). These drugs are designed on the molecular

Table 1. Treatment options for advanced/metastatic pRCC patients

	Drug	Class	Target
First-line treatment	Savolitinib [94]	TKI	MET
	Pembrolizumab [105■]	ICI	PD-1 receptor
	Cabozantinib [93]	TKI	MET, RET, AXL, VEGFR2, FLT3, c-KIT
	Sunitinib [110]	TKI	PDGR, VEGF-R, CD117
Second-line treatment	Everolimus [111]	TKI	mTOR
	Tivozanib [98]	TKI	VEGF-1, VEGF-2, VEGF-3, c-kit, PDGR
Other treatment	Tivantinib [96]	TKI	c-MET
	Erlotinib [97]	TKI	EGFR

pRCC, papillary renal cell carcinoma. First- and second-line treatment options for pRCC patients based on the latest ESMO guidelines [95■■]. For each compound, the class of action (Tyrosine Kinase Inhibitors or Immune checkpoint inhibitors) and the drug targets are shown.

consequences of the inactivation of the tumour suppressor gene *VHL*, the most common alteration on ccRCC but less frequent in pRCC. Therefore, treatment of nonccRCCs with these compounds showed reduced effectiveness and low response rate [103].

The efficacy of the PD1 inhibitor, Pembrolizumab, was tested for the first time in 2021 on 165 nonccRCCs in a phase II clinical trial (ClinicalTrials.gov identifier: NCT02853344). The results showed promising clinical activity in the overall nonccRCC population: in particular, better overall response was detected in pRCC patients compared to chRCC, the third major RCC subtype. The clinical responses correlate with high PD-L1 expression [104,105■]. According to these results, Pembrolizumab was introduced as a first-line treatment option for pRCC. Nivolumab alone or in combination with the VEGF inhibitor, Cabozantinib, also showed promising efficacy in pRCC [106–108]. Alternative first or second-line treatment options for nonccRCCs also include mTOR-targeted therapies such as Cabozantinib, Sunitinib, Pazopanib and Everolimus [109–111]. Importantly, nonccRCC showed a worse response to these compounds and shorter survival compared to advanced ccRCC. Robust evidence is missing for third-line treatment strategies [95■■,99]. These findings suggest that specific molecular characteristics in different subsets of pRCC can determine different targeting approaches.

CONCLUSION

To conclude, continuing studying the diverse morphologies of pRCC and respective molecular alterations, and establishing important genotype-phenotype correlations will contribute to a better risk stratification of patients with pRCC, enabling the discovery of prognostic biomarkers. This will lead to more targeted and personalised treatment strategies for these nonccRCC renal cancer patients.

Acknowledgements

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest
■■ of outstanding interest

1. Padala SA, Barsouk A, Thandra KC, *et al.* Epidemiology of renal cell carcinoma. World J Oncol 2020; 11:79–87.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71:7–33.
3. Dy GW, Gore JL, Forouzanfar MH, *et al.* Global burden of urologic cancers, 1990–2013. Eur Urol 2017; 71:437–446.
4. Capitanio U, Bensalah K, Bex A, *et al.* Epidemiology of renal cell carcinoma. Eur Urol 2019; 75:74–84.
5. Makhov P, Joshi S, Ghatalia P, *et al.* Resistance to systemic therapies in clear cell renal cell carcinoma: mechanisms and management strategies. Mol Cancer Ther 2018; 17:1355–1364.
6. Beksac AT, Paulucci DJ, Blum KA, *et al.* Heterogeneity in renal cell carcinoma. Urol Oncol 2017; 35:507–515.
7. Moch H, Humphrey P, Ulbright T, Reuter V. WHO Classification of Tumours of the Urinary System and Male Genital Organs. 4th Edition Lyon: International Agency for Research on Cancer (IARC); 2016.
8. Vera-Badillo FE, Templeton AJ, Duran I, *et al.* Systemic therapy for nonclear cell renal cell carcinomas: a systematic review and meta-analysis. Eur Urol 2015; 67:740–749.
9. Steffens S, Janssen M, Roos FC, *et al.* Incidence and long-term prognosis of papillary compared to clear cell renal cell carcinoma–a multicentre study. Eur J Cancer 2012; 48:2347–2352.
10. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. Mod Pathol 1997; 10:537–544.
11. Jiang F, Richter J, Schraml P, *et al.* Chromosomal imbalances in papillary renal cell carcinoma: genetic differences between histological subtypes. Am J Pathol 1998; 153:1467–1473.
12. Ricketts CJ, De Cubas AA, Fan H, *et al.* The cancer genome atlas comprehensive molecular characterization of renal cell carcinoma. Cell Rep 2018; 23:3698.
13. Saleeb RM, Plant P, Tawedrous E, *et al.* Integrated phenotypic/genotypic analysis of papillary renal cell carcinoma subtypes: identification of prognostic markers, cancer-related pathways, and implications for therapy. Eur Urol Focus 2018; 4:740–748.
14. Cancer Genome Atlas Research Network. Linehan WM, Spellman PT, Ricketts CJ, *et al.* Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med 2016; 374:135–145.
15. Wong ECL, Di Lena R, Breau RH, *et al.* Morphologic subtyping as a prognostic predictor for survival in papillary renal cell carcinoma: Type 1 vs. type 2. Urol Oncol 2019; 37:721–726.
16. Delahunt B, Eble JN, McCredie MR, *et al.* Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. Hum Pathol 2001; 32:590–595.
17. Pan H, Ye L, Zhu Q, *et al.* The effect of the papillary renal cell carcinoma subtype on oncological outcomes. Sci Rep 2020; 10:21073.
18. Le X, Wang XB, Zhao H, *et al.* Comparison of clinicopathologic parameters and oncologic outcomes between type 1 and type 2 papillary renal cell carcinoma. BMC Urol 2020; 20:148.
19. Saleeb RM, Brimo F, Farag M, *et al.* Toward biological subtyping of papillary renal cell carcinoma with clinical implications through histologic, immunohistochemical, and molecular analysis. Am J Surg Pathol 2017; 41:1618–1629.
20. Lobo J, Ohashi R, Helmchen BM, *et al.* The morphological spectrum of
■ papillary renal cell carcinoma and prevalence of provisional/emerging renal tumor entities with papillary growth. Biomedicines 2021; 9:.
This original paper presents an analysis of the prevalence of new and emerging renal cancer entities with papillary features.
21. Trpkov K, Williamson SR, Gill AJ, *et al.* Novel, emerging and provisional renal
■■ entities: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol 2021; 34:1167–1184.
This comprehensive review paper covers recent proposed entities in renal cancer, including those with papillary features.
22. Cimadamore A, Cheng L, Scarpelli M, *et al.* Towards a new WHO classifica-
■ tion of renal cell tumor: what the clinician needs to know-a narrative review. Transl Androl Urol 2021; 10:1506–1520.
This review summarises the most remarkable changes in classification and histological features of renal cancer, including pRCC, which have clinical implications for treatment and follow-up.
23. Trpkov K, Hes O, Williamson SR, *et al.* New developments in existing WHO entities and evolving molecular concepts: The Genitourinary Pathology Society (GUPS) update on renal neoplasia. Mod Pathol 2021; 34:1392–1424.
24. Trpkov K, Hes O. New and emerging renal entities: a perspective post-WHO 2016 classification. Histopathology 2019; 74:31–59.

25. Sarungbam J, Mehra R, Tomlins SA, *et al.* Tubulocystic renal cell carcinoma: a distinct clinicopathologic entity with a characteristic genomic profile. Mod Pathol 2019; 32:701–709.

26. Williamson SR, Eble JN, Cheng L, Grignon DJ. Clear cell papillary renal cell carcinoma: differential diagnosis and extended immunohistochemical profile. Mod Pathol 2013; 26:697–708.

27. Wyvekens N, Valtcheva N, Mischo A, *et al.* Novel morphological and genetic features of fumarate hydratase deficient renal cell carcinoma in HLRCC syndrome patients with a tailored therapeutic approach. Genes Chromosom Cancer 2020; 59:611–619.

28. Wyvekens N, Rechsteiner M, Fritz C, *et al.* Histological and molecular characterization of TFEB-rearranged renal cell carcinomas. Virchows Arch 2019; 474:625–631.

29. Eble JN, Delahunt B. Emerging entities in renal cell neoplasia: thyroid-like follicular renal cell carcinoma and multifocal oncocytoma-like tumours associated with oncocytosis. Pathology 2018; 50:24–36.

30. Siadat F, Trpkov K. ESC, ALK, HOT and LOT: three letter acronyms of emerging renal entities knocking on the door of the who classification. Cancers 2020; 12:.

31. Sirohi D, Smith SC, Agarwal N, Maughan BL. Unclassified renal cell carcinoma: diagnostic difficulties and treatment modalities. Res Rep Urol 2018; 10:205–217.

32. Perrino CM, Grignon DJ, Williamson SR, *et al.* Morphological spectrum of renal cell carcinoma, unclassified: an analysis of 136 cases. Histopathology 2018; 72:305–319.

33. Srigley JR, Delahunt B, Eble JN, *et al.* The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013; 37:1469–1489.

34. Trpkov K, Hes O, Agaimy A, *et al.* Fumarate hydratase-deficient renal cell carcinoma is strongly correlated with fumarate hydratase mutation and hereditary leiomyomatosis and renal cell carcinoma syndrome. Am J Surg Pathol 2016; 40:865–875.

35. Lau HD, Chan E, Fan AC, *et al.* A Clinicopathologic and molecular analysis of fumarate hydratase-deficient renal cell carcinoma in 32 patients. Am J Surg Pathol 2020; 44:98–110.

36. Moch H, Ohashi R, Gandhi JS, Amin MB. Morphological clues to the appropriate recognition of hereditary renal neoplasms. Semin Diagn Pathol 2018; 35:184–192.

37. Gleeson JP, Nikolovski I, Dinatale R, *et al.* Comprehensive molecular characterization and response to therapy in fumarate hydratase-deficient renal cell carcinoma. Clin Cancer Res 2021; 27:2910–2919.

38. Carril-Ajuria L, Colomba E, Cerbone L, *et al.* Response to systemic therapy in fumarate hydratase-deficient renal cell carcinoma. Eur J Cancer 2021; 151:106–114.

39. Argani P. MiT family translocation renal cell carcinoma. Semin Diagn Pathol 2015; 32:103–113.

40. Smith NE, Illei PB, Allaf M, *et al.* t(6;11) renal cell carcinoma (RCC): expanded immunohistochemical profile emphasizing novel RCC markers and report of 10 new genetically confirmed cases. Am J Surg Pathol 2014; 38:604–614.

41. Green WM, Yonescu R, Morsberger L, *et al.* Utilization of a TFE3 break-apart FISH assay in a renal tumor consultation service. Am J Surg Pathol 2013; 37:1150–1163.

42. Argani P, Lae M, Hutchinson B, *et al.* Renal carcinomas with the t(6;11)(p21; q12): clinicopathologic features and demonstration of the specific alpha-TFEB gene fusion by immunohistochemistry, RT-PCR, and DNA PCR. Am J Surg Pathol 2005; 29:230–240.

43. Argani P, Reuter VE, Zhang L, *et al.* TFEB-amplified renal cell carcinomas: an aggressive molecular subset demonstrating variable melanocytic marker expression and morphologic heterogeneity. Am J Surg Pathol 2016; 40:1484–1495.

44. Hang JF, Chung HJ, Pan CC. ALK-rearranged renal cell carcinoma with a novel PLEKHA7-ALK translocation and metanephric adenoma-like morphology. Virchows Arch 2020; 476:921–929.

45. Sukov WR, Hodge JC, Lohse CM, *et al.* ALK alterations in adult renal cell carcinoma: frequency, clinicopathologic features and outcome in a large series of consecutively treated patients. Mod Pathol 2012; 25: 1516–1525.

46. Tao JJ, Wei G, Patel R. ALK fusions in renal cell carcinoma: response to entrectinib. JCO Precis Oncol 2018; 2:1–8.

47. Petersson F, Bulimbasic S, Hes O, *et al.* Biphasic alveolosquamoid renal carcinoma: a histomorphological, immunohistochemical, molecular genetic, and ultrastructural study of a distinctive morphologic variant of renal cell carcinoma. Ann Diagn Pathol 2012; 16:459–469.

48. Suarez-Vilela D, Izquierdo FM. CD57 in biphasic squamoid alveolar renal cell carcinoma. Pathol Int 2020; 70:56–57.

49. Zhou L, Xu H, Zhou Y, *et al.* Biphasic squamoid alveolar renal carcinoma with positive CD57 expression: a clinicopathologic study of three cases. Pathol Int 2019; 69:519–525.

50. Hes O, Condom Mundo E, Peckova K, *et al.* Biphasic squamoid alveolar renal cell carcinoma: a distinctive subtype of papillary renal cell carcinoma? Am J Surg Pathol 2016; 40:664–675.

51. Suárez-Vilela D, Izquierdo FM, Méndez-Álvarez JR, Velasco-Alonso J. The squamoid cells in biphasic squamoid alveolar renal carcinoma present cytophagocytosis (not emperipolesis) of apoptotic neutrophilic granulocytes. Am J Surg Pathol 2018; 42:420–422.

52. Chartier S, Mejean A, Richard S, *et al.* Biphasic squamoid alveolar renal cell carcinoma: 2 cases in a family supporting a continuous spectrum with papillary Type I renal cell carcinoma. Am J Surg Pathol 2017; 41:1011–1012.

53. Denize T, Just PA, Sibony M, *et al.* MET alterations in biphasic squamoid alveolar papillary renal cell carcinomas and clinicopathological features. Mod Pathol 2021; 34:647–659.

54. Argani P, Reuter VE, Eble JN, *et al.* Biphasic hyalinizing psammomatous renal cell carcinoma (BHP RCC): a distinctive neoplasm associated with somatic NF2 mutations. Am J Surg Pathol 2020; 44:901–916.

55. Yakirevich E, Pavlick DC, Perrino CM, *et al.* NF2 tumor suppressor gene inactivation in advanced papillary renal cell carcinoma. Am J Surg Pathol 2021; 45:716–718.

56. Kim SS, Cho YM, Kim GH, *et al.* Recurrent KRAS mutations identified in papillary renal neoplasm with reverse polarity-a comparative study with papillary renal cell carcinoma. Mod Pathol 2020; 33:690–699.

57. Wei S, Kutikov A, Patchefsky AS, *et al.* Papillary renal neoplasm with reverse polarity is often cystic: report of 7 cases and review of 93 cases in the literature. Am J Surg Pathol 2021.

58. Kiyozawa D, Kohashi K, Takamatsu D, *et al.* Morphological, immunohistochemical, and genomic analyses of papillary renal neoplasm with reverse polarity. Hum Pathol 2021; 112:48–58.

59. Chang HY, Hang JF, Wu CY, *et al.* Clinicopathological and molecular characterisation of papillary renal neoplasm with reverse polarity and its renal papillary adenoma analogue. Histopathology 2021; 78:1019–1031.

60. Zhou L, Xu J, Wang S, *et al.* Papillary renal neoplasm with reverse polarity: a clinicopathologic study of 7 cases. Int J Surg Pathol 2020; 28:728–734.

61. Al-Obaidy KI, Eble JN, Cheng L, *et al.* Papillary renal neoplasm with reverse polarity: a morphologic, immunohistochemical, and molecular study. Am J Surg Pathol 2019; 43:1099–1111.

62. Lee HJ, Shin DH, Park JY, *et al.* Unilateral synchronous papillary renal neoplasm with reverse polarity and clear cell renal cell carcinoma: a case report with KRAS and PIK3CA mutations. Diagn Pathol 2020; 15:123.

63. Al-Obaidy KI, Eble JN, Nassiri M, *et al.* Recurrent KRAS mutations in papillary renal neoplasm with reverse polarity. Mod Pathol 2020; 33:1157–1164.

64. Skenderi F, Ulamec M, Vanecek T, *et al.* Warthin-like papillary renal cell carcinoma: clinicopathologic, morphologic, immunohistochemical and molecular genetic analysis of 11 cases. Ann Diagn Pathol 2017; 27:48–56.

65. Alaghehbandan R, Michal M, Kuroda N, Hes O. Thyroid-like follicular carcinoma of the kidney: an emerging renal neoplasm with curiously misplaced histologic features. A case report. Int J Surg Pathol 2017; 25:379–380.

66. Jindal T, Roy P, Subedi N. Thyroid like follicular renal cell carcinoma: a rare entity. Indian J Pathol Microbiol 2021; 64:594–595.

67. Li C, Dong H, Fu W, *et al.* Thyroid-like follicular carcinoma of the kidney and papillary renal cell carcinoma with thyroid-like feature: comparison of two cases and literature review. Ann Clin Lab Sci 2015; 45:707–712.

68. Al-Obaidy KI, Bridge JA, Cheng L, *et al.* EWSR1-PATZ1 fusion renal cell carcinoma: a recurrent gene fusion characterizing thyroid-like follicular renal cell carcinoma. Mod Pathol 2021.

69. Perret R, Lefort F, Bernhard JC, *et al.* Thyroid-like follicular renal cell carcinoma with sarcomatoid differentiation and aggressive clinical course: a case report confirming EWSR1::PATZ1 fusion. Histopathology 2021.

70. Ko JJ, Grewal JK, Ng T, *et al.* Whole-genome and transcriptome profiling of a metastatic thyroid-like follicular renal cell carcinoma. Cold Spring Harb Mol Case Stud 2018; 4:.

71. Kovacs G, Akhtar M, Beckwith BJ, *et al.* The Heidelberg classification of renal cell tumours. J Pathol 1997; 183:131–133.

72. Kovac M, Navas C, Horswell S, *et al.* Recurrent chromosomal gains and heterogeneous driver mutations characterise papillary renal cancer evolution. Nat Commun 2015; 6:6336.

73. Zhu B, Poeta ML, Costantini M, *et al.* The genomic and epigenomic evolutionary history of papillary renal cell carcinomas. Nat Commun 2020; 11:3096.
■

This work investigates the intra-tumour heterogeneity and tumor evolution of pRCCs providing a comprehensive characterisation of the molecular background of this tumour subtype.

74. Pitra T, Pivovarcikova K, Alaghehbandan R, Hes O. Chromosomal numerical aberration pattern in papillary renal cell carcinoma: Review article. Ann Diagn Pathol 2019; 40:189–199.

75. Marsaud A, Dadone B, Ambrosetti D, *et al.* Dismantling papillary renal cell carcinoma classification: The heterogeneity of genetic profiles suggests several independent diseases. Genes Chromosom Cancer 2015; 54:369–382.

76. Schraml P, Müller D, Bednar R, *et al.* Allelic loss at the D9S171 locus on chromosome 9p13 is associated with progression of papillary renal cell carcinoma. J Pathol 2000; 190:457–461.

77. Haake SM, Weyandt JD, Rathmell WK. Insights into the genetic basis of the renal cell carcinomas from The Cancer Genome Atlas. Mol Cancer Res 2016; 14:589–598.

78. Durinck S, Stawiski EW, Pavia-Jimenez A, *et al.* Spectrum of diverse genomic alterations define nonclear cell renal carcinoma subtypes. Nat Genet 2015; 47:13–21.
79. Pal SK, Geynisman DM, Ali SM, *et al.* Comprehensive genomic profiling (CGP) of advanced papillary renal cell carcinoma (PRCC) to reveal distinctions from TCGA dataset. Am Soc Clin Oncol 2017.
80. Han Y. Analysis of the role of the Hippo pathway in cancer. J Transl Med 2019; 17:116.
81. Sourbier C, Liao PJ, Ricketts CJ, *et al.* Targeting loss of the Hippo signaling pathway in NF2-deficient papillary kidney cancers. Oncotarget 2018; 9:10723–10733.
82. Zou Z, Tao T, Li H, Zhu X. mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. Cell Biosci 2020; 10:31.
83. Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene 2005; 24:2899–2908.
84. Garje R, Elhag D, Yasin HA, *et al.* Comprehensive review of chromophobe renal cell carcinoma. Crit Rev Oncol Hematol 2021; 160:103287.
85. Pang JS, Li ZK, Lin P, *et al.* The underlying molecular mechanism and potential drugs for treatment in papillary renal cell carcinoma: a study based on TCGA and Cmap datasets. Oncol Rep 2019; 41:2089–2102.
86. Malouf GG, Ali SM, Wang K, *et al.* Genomic characterization of renal cell carcinoma with sarcomatoid dedifferentiation pinpoints recurrent genomic alterations. Eur Urol 2016; 70:348–357.
87. Li F, Aljahdali IAM, Zhang R, *et al.* Kidney cancer biomarkers and targets for therapeutics: survivin (BIRC5), XIAP, MCL-1, HIF1alpha, HIF2alpha, NRF2, MDM2, MDM4, p53, KRAS and AKT in renal cell carcinoma. J Exp Clin Cancer Res 2021; 40:254.
88. Kensler TW, Wakabayashi N, Biswal S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu Rev Pharmacol Toxicol 2007; 47:89–116.
89. Cloer EW, Goldfarb D, Schrank TP, *et al.* NRF2 activation in cancer: from DNA to protein. Cancer Res 2019; 79:889–898.
90. Balamurugan K, Luu V, Kaufmann M, *et al.* Onconeuronal cerebellar degeneration-related antigen, Cdr2, is strongly expressed in papillary renal cell carcinoma and leads to attenuated hypoxic response. Oncogene 2009; 28:3274–3285.
91. Brodziak A, Sobczuk P, Bartnik E, *et al.* Drug resistance in papillary RCC: from putative mechanisms to clinical practicalities. Nat Rev Urol 2019; 16:655–673.
92. Albiges L, Guegan J, Le Formal A, *et al.* MET is a potential target across all papillary renal cell carcinomas: result from a large molecular study of pRCC with CGH array and matching gene expression array. Clin Cancer Res 2014; 20:3411–3421.
93. Grullich C. Cabozantinib: multikinase inhibitor of MET, AXL, RET, and VEGFR2. Recent Results Cancer Res 2018; 211:67–75.
94. Choueiri TK, Plimack E, Arkenau HT, *et al.* Biomarker-based Phase II trial of savolitinib in patients with advanced papillary renal cell cancer. J Clin Oncol 2017; 35:2993–3001.
95. Powles T, Albiges L, Bex A, *et al.* ESMO Clinical Practice Guideline update
■■ on the use of immunotherapy in early stage and advanced renal cell carcinoma. Ann Oncol 2021; 32:1511–1519.

This paper has described the most recent updates on the treatment of renal cell carcinoma. It also indicates the therapeutical guidelines to cure patients affected by pRCC.

96. Twardowski PW, Tangen CM, Wu X, *et al.* Parallel (Randomized) Phase II evaluation of tivantinib (ARQ197) and tivantinib in combination with erlotinib in papillary renal cell carcinoma: SWOG S1107. Kidney Cancer 2017; 1:123–132.
97. Luo J, Makhnin A, Tobi Y, *et al.* Erlotinib and trametinib in patients with EGFR-mutant lung adenocarcinoma and acquired resistance to a prior tyrosine kinase inhibitor. JCO Precis Oncol 2021; 5.
98. Hepgur M, Sadeghi S, Dorff TB, Quinn DI. Tivozanib in the treatment of renal cell carcinoma. Biologics 2013; 7:139–148.
99. Ahrens M, Scheich S, Hartmann A, *et al.* Non-clear cell renal cell carcinoma – pathology and treatment options. Oncol Res Treat 2019; 42:128–135.
100. Diaz-Montero CM, Rini BI, Finke JH. The immunology of renal cell carcinoma. Nat Rev Nephrol 2020; 16:721–735.
101. Bi K, He MX, Bakouny Z, *et al.* Tumor and immune reprogramming during immunotherapy in advanced renal cell carcinoma. Cancer Cell 2021; 39:649–661; e5.
102. Braun DA, Street K, Burke KP, *et al.* Progressive immune dysfunction with advancing disease stage in renal cell carcinoma. Cancer Cell 2021; 39:632–648; e8.
103. Escudier B, Porta C, Schmidinger M, *et al.* Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2019; 30:706–720.
104. Marchetti A, Rosellini M, Mollica V, *et al.* The molecular characteristics of non-clear cell renal cell carcinoma: what's the story morning glory? Int J Mol Sci 2021; 22:.
105. McDermott DF, Lee JL, Ziobro M, *et al.* Open-label, single-arm, Phase II study
■ of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. J Clin Oncol 2021; 39:1029–1039.

This paper summarises the results of a clinical trial conducted on pRCC patients to evaluate the effect of the PD1 inhibitor Pembrolizumab.

106. McKay RR, Bosse D, Xie W, *et al.* The clinical activity of PD-1/PD-L1 inhibitors in metastatic non-clear cell renal cell carcinoma. Cancer Immunol Res 2018; 6:758–765.
107. Lee C-H, Voss MH, Carlo MI, *et al.* Nivolumab plus cabozantinib in patients with nonclear cell renal cell carcinoma: Results of a phase 2 trial. Wolters Kluwer Health; 2021.
108. Koshkin VS, Barata PC, Zhang T, *et al.* Clinical activity of nivolumab in patients with nonclear cell renal cell carcinoma. J Immunother Cancer 2018; 6:9.
109. Martinez Chanza N, Xie W, Asim Bilen M, *et al.* Cabozantinib in advanced nonclear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. Lancet Oncol 2019; 20:581–590.
110. Ravaud A, Oudard S, De Fromont M, *et al.* First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG)dagger. Ann Oncol 2015; 26:1123–1128.
111. Buti S, Leonetti A, Dallatomasina A, Bersanelli M. Everolimus in the management of metastatic renal cell carcinoma: an evidence-based review of its place in therapy. Core Evid 2016; 11:23–36.