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REVIEW

The Tumor Entity Denominated "*clear cell-papillary renal cell carcinoma*" According to the WHO 2016 new Classification, have the Clinical Characters of a Renal Cell Adenoma as does Harbor a Benign Outcome

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Abstract The new WHO 2016 classification of renal neoplasia encounters the new entity called "clear cell papillary renal cell carcinoma" (ccpRCC). The ccpRCC has been long included as a subtype of clear cell RCC histotype and it actually ranges from 2 to 9% in different routinely available cohort of renal carcinomas. Of important note, ccpRCC does not show any recurrences or metastases or lymph-node invasion and the outcome is always good. We reviewed twenty-four publications with available follow-up for patients (no. 362) affected by clear cell papillary RCCs/renal adenomatoid tumours and notably ccpRCC harbors an indolent clinical behavior after a mean of 38 months (3,5 years) of follow-up. This paper reviews the histological, molecular and clinical features characterizing ccpRCC, with the goal of focusing the knowledge of the benign fashion of this new tumour entity, supporting the idea of a new renal cell adenoma recruited morphologically from ex conventional clear cell RCC tumours.

Keywords Clear cell papillary RCC · Renal adenomatoid tumour (RAT) · WHO 2016 classification of renal neoplasia · Renal adenoma · Benign

Introduction

Clear cell papillary RCC (ccpRCC) has been recently introduced as a new tumour entity by the 2016 WHO classification of renal neoplasia [1]. Overall, renal cancer comprises a het-

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erogeneous group of malignancies with different morphological and immunohistochemical features, genetic aberrations, and peculiar clinical behavior. The 2016 WHO classification of renal tumours describes more than 40 different histological subtypes, being clear cell renal cell carcinoma (ccRCC) the most frequent subtype (accounting for about 70–85% of renal epithelial cancers), followed by papillary RCC and chromophobe RCC [1]. In 2013, the International Society of Urological Pathology (ISUP) added five new histological entities: tubolocystic RCC, acquired cystic disease-associated RCC, the microphthalmia transcription factor (MiT)-family translocation RCCs [in particular t(6;11) RCC], hereditary leiomyomatosis syndrome-associated RCC, and clear cell (tubulo)papillary RCC [2]. Initially described by Tickoo et al. [3] as a neoplasm occurring in end-stage renal disease (ESRD) setting, ccpRCC arises mainly in patients with no functional kidney impairments as a sporadic tumor [4–8]. Notably, clear cell papillary RCC has been reported without any tumor recurrences or metastases with the major limitation represented by the cumulative years of follow-up. For these reasons the term carcinoma has been maintained.

In this review we focused on ccpRCC at all clinico-pathological levels, with the goal to highlight the absence of recurrences or metastases reported, clustering ccpRCC in the group of renal cell adenoma.

Materials & Methods

A comprehensive literature search was conducted independently by two authors (C.C. and L.C.) from the PubMed database. The following keywords were used: clear cell papillary renal cell carcinoma, clear cell tubulo-papillary renal cell carcinoma, renal adenomatoid tumours of the kidney. We limited our research to articles written in English and we included only studies with available follow-up. Twenty-four articles were selected.

Clinical Presentation & Epidemiology

Clinically, the age at presentation of ccpRCC does not differ from that of RCCs (mean 60 years; ranging from 18 to 88 years), with no sex predilection [2, 5, 8]. The diagnosis generally follows the incidental finding of a renal mass in a completely asymptomatic patient.

Clear cell papillary RCC is considerably an under-recognized epidemiological entity despite it being a relative common renal neoplasm, accounting for 1.9 to 4.1% [9–11] of all epithelial renal cell carcinomas representing the fourth most frequent RCC histotype [12].

Overall, ccpRCC is not uncommon among small low-grade RCC tumors, it can be correctly recognized by its unique histomorphological features and confirmed by routinely immunohistochemical analysis, and it has an excellent clinical outcome following resection [13].

Among the manuscript we reported clinico-pathological data on ccpRCC and renal adenomatoid tumours of the kidney (RAT) being considered by the WHO 2016 two synonyms (Tables 1 and 2).

Pathologic Features

Macroscopic Features

Clear cell papillary RCC usually presents as a small unicentric, unilateral, clearly circumscribed and well-encapsulated mass located in the kidney cortex [2, 12]. On gross examination, tumor can be completely solid, or exhibit cystic changes ranging from 10% to 95% of the tumor mass [14–16]. The majority of ccpRCC reported in literature is in pathological stage T1 (generally less than 4 cm – T1a tumor), with few pT2 tumors, rarely pT3a [8, 9, 17].

Macroscopic features are showed in Fig. 1a.

Microscopic Characteristics

The most frequent architecture is the tubular-papillary, consisting of branching tubules and papillary projections [18]. Papillae can be rounded and small, or with branching contours. However, more complex architectures have been reported. Usually, a single layer of neoplastic cells with clear cell cytoplasm covers the papillae.

The tubular pattern may also predominates [19] and tubules show heterogeneous shapes and sizes [8].

Cystic component is present in almost all ccpRCC. The tumor structure can be mainly solid, with the cysts confined

Table 1 Clear cell papillary RCC/RAT versus clear cell RCC

	Clear cell-papillary RCC/RAT	Clear cell RCC
Morphology		
clear cell	present	present
nuclei aligned	present	not present
Immunohistochemistry		
CK7	present, diffuse	rare
CK34bE12	present, diffuse	rare
GATA-3	present*	absent
Molecular biology		
VHL mutation	absent all	present most
Genomics	flat DNA	complex
Outcome	benign	malignant

*30% of cases

Table 2 Clear cell papillary RCC/RAT of the kidney according to WHO 2016 classification. No tumour recurrences or metastases being reported at the median follow-up time of 38 months (3,5 years) in 362 patients

	Patients N.	Stage	Follow-up		Tumor Recurrence/ Metastasis
			Range (months)	Mean (months)	
Tickoo et al.	15 (52 tumors)	pT1 N0 M0	9–94 (15 cases)	34	No*
Aron et al.	64	pT1a N0 M0 (51 cases) pT1b N0 M0 (5 cases) pT2a N0 M0 (2 cases) pT3a N0 M0 (2 cases)	18–180 (30 cases)	47	No**
Gobbo et al.	5	pT1 N0 M0	1–48 (5 cases)	24.2	No
Aydin et al.	33 (36 tumors)	pT1a N0 M0 (34 cases) pT1b N0 M0 (2 cases)	1–85 (20 cases)	27.4	No
Williamson et al.	34 (55 tumors)	pT1a NX MX (53 cases) pT1b NX MX (1 case) pT2 NX MX (1 case)	3–108 (18 cases)	54	No***
Rao et al.	3	pT1 N0 M0	36–60 (3 cases)	NA	No
Park et al.	15	pT1a NX M0	9–29 (15 cases)	15.6	No
Michal et al.	1 RAT	pT2 N0 M0	-	6	No
Michal et al.	5 RAT	pT1a NX MX (3 cases) pT1b NX MX (1 case) pT2a NX MX (1 case)	8–29 (4 cases)	14.5	No
Mai et al.	10 (21 tumors)	NA	12–120 (10 cases)	36	No
Deml et al.	27	pT1 N0 M0 (25 cases) pT2a N0 M0 (1 case) NA (1 case)	7–84 (21 cases)	29.7	No
	7 RAT	pT1 N0 M0 NA (1 case)	25–38 (5 cases)	32.3	No
Zhou et al.	12	pT1 N0 M0	6–35 (12 cases)	19	No
Alexiev et al.	5 (6 tumors) ccpRCC/RAT	pT1a NX MX	23–72 (5 cases)	39	No
Alexiev et al.	21	pT1a NX MX (19 cases) pT1b NX MX (2 cases)	3–73 (11 cases)	39	No
Bhatnagar et al.	14	pT1 N0 M0	NA	NA	No
Shi et al.	11	pT1 N0 M0	16–132 (8 cases)	71.75	No
Rohan et al.	9	pT1a NX MX	NA	NA	No
Leroy et al.	42	pT1 N0 M0	10–72 (42 cases)	NA	No
Lawrie et al.	17	NA	3–157 (10 cases)	29.3	No
Wolfe et al.	1	pT1a N0 M0	-	17	No
Yan et al.	6	pT1 N0 M0	13–55 (6 cases)	22.8	No
Diolombi et al.	58	pT1a NX MX (46 cases) pT1b NX MX (7 cases) pT2a NX MX (1 case) pT2b NX MX (1 case) pT3 NX MX (1 case)	1–175 (58 cases)	21	No****

Table 2 (continued)

	Patients N.	Stage	Follow-up		Tumor Recurrence/ Metastasis
			Range (months)	Mean (months)	
Dhakal et al.	21	pT1a NX MX (19 cases) pT2a NX MX (2 cases)	12–183 (20 cases)	80	No
Martignoni et al. "present study"	11	pT1a NX MX (9 cases) pT1b NX MX (2 cases)	7–96 (11 cases)	58	No*****

NA, not available *ccpRCC* clear cell papillary renal cell carcinoma *RAT* renal adenomatoid tumor

* One patient died of metastatic disease within 34 months of diagnosis, 2 others had regional lymph node metastasis at the time of nephrectomy. In each of these 3 patients the dominant tumor was an acquired cystic disease – associated RCC (and not clear cell papillary RCC)

**One case with evidence of controlateral tumor 78 months after the initial resection. No histologic diagnosis was performed at the time of the study (84 months of follow/up); therefore the nature of this lesion is uncertain

***Three patients at the time of most recent follow-up had new renal masses, without tissue diagnosis

****One patient was presumed to have contralateral disease on the basis of imaging findings and is alive and well 37 months after multiple partial nephrectomies. Metastatic disease to the lung was clinically presumed in 1 patient in whom a higher-grade lesion may have been missed during sampling of the predominantly cystic pT1b tumor and tissue confirmation of the metastases was not obtained. Another case presented with multiple skeletal and pulmonary metastases 8 months after resection of pT3 ccpRCC with sarcomatoid differentiation

*****One case occurred after kidney transplantation and was diagnosed as de novo renal neoplasia

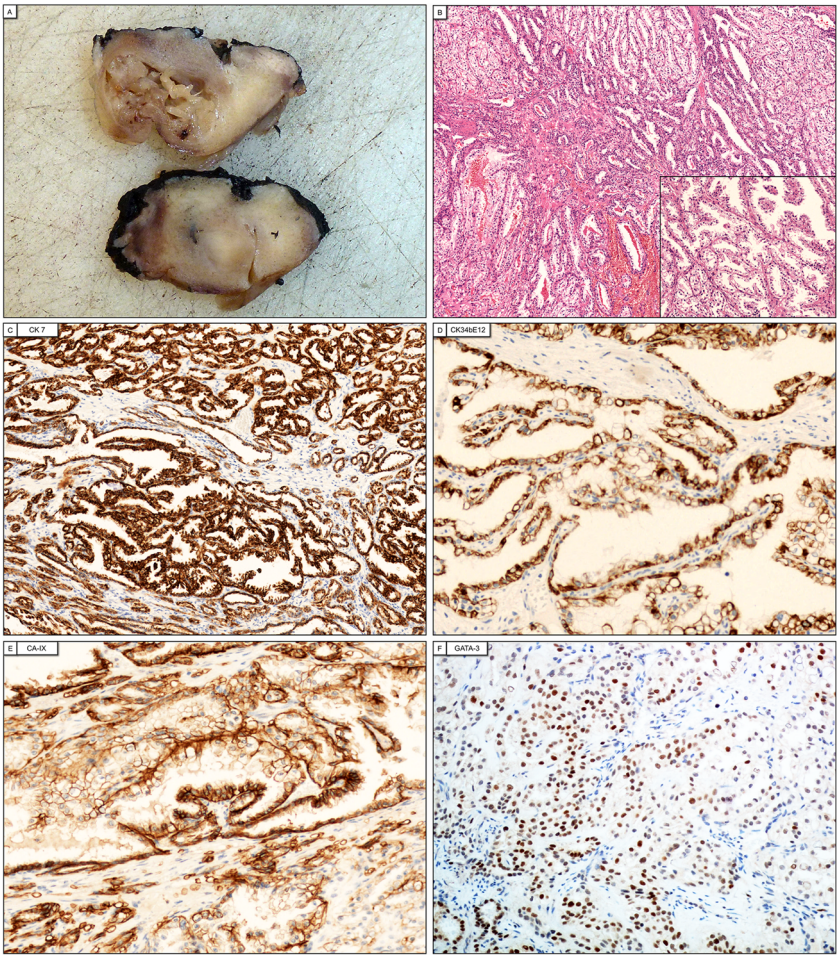

Fig. 1 Clear cell-papillary RCC. Gross finding (**a**), haematoxylin and eosin staining (**b**), diffuse CK7 immunoexpression (**c**), strong high molecular weight cytokeratin (34bE12) (**d**), CAIX baso-lateral expression (**e**) and GATA-3 nuclear staining (**f**)

to the periphery of the mass, or predominantly cystic, with the peculiar papillae focally protruding within the cystic lumen.

Microscopic architecture is showed in Fig. 1b.

The cells lining the papillae and the cystic spaces are cuboidal, small to medium in size, typically with moderate to abundant optically clear cytoplasm. Characteristically, the nuclei, universally of low Fuhrman and low ISUP/WHO grade (small, round, with a regular border, often hyperchromatic, and uniform in shape, with inconspicuous nucleoli - grade 1 or 2), are typically localized in a linear fashion toward the luminal surface in the upper part of the cells and away from the basement membrane [5, 6, 13, 14, 20, 21].

Clear cell papillary RCC usually has a prominent stromal component made by fibrotic or collagenous tissue, with thin, fusiform nuclei, and small blood vessels finely scattered. When the stromal hyalinization is prominent can subvert and mask the entire epithelial component, making the histological diagnosis difficult [4].

Among aforementioned context, a tumour entity described by Michal Michal was initially reported and denominated renal adenomatoid tumour (RAT) [22].

Distinctive features of RAT include: 1) The angioleiomyomatous stroma, the amount of which may vary widely from less than 10% to involve the entire tumor, organized in bundles surrounding the entire tumor and supporting the epithelial tubular structures; 2) The epithelium characterized by secretory cells, with apical clear snouts, imparting to the glands the distinctive appearance of a "shark smile". The basophilic nuclei present a low-grade (Fuhrman grades 1 and 2) and aligned in a basal position next to the basal membrane [23–25].

Morphological features along with immunohistochemical and molecular characteristics and the common benign biological behavior shared by ccpRCC and RAT lead to the hypothesis that these two originally distinct tumors represent actually morphological variants of the same cancer entity [18, 26]. The new WHO 2016 renal neoplasia classification have noted the inclusion of the RAT into the ccpRCC category after a consensus conference.

Immunohistochemical Features

The tumor shows diffuse and uniform immunoreactivity for CK7, with a co-expression of CA-IX [3, 6, 8, 11]. CK7 staining appears diffusely strong at cysts, papillae,

and tubules/acini (Fig. 1c); CK7 positivity is also detectable, albeit of weaker intensity, in clear cell nests. The typical CAIX expression pattern in ccpRCC, with a diffuse membrane distribution lacking luminal borders staining (cup-shaped distribution) [3] (Fig. 1e), aids in the differential diagnosis with ccRCC [18]. Moreover, the majority of tumor cells strongly labels for high-molecular weight cytokeratin (34βE12) [19] (Fig. 1d), paired box gene 2 (PAX2), PAX8, vimentin, E-cadherin, β-catenin, c-MET, CK19, p27, p53. A strong immunostaining for HIF1 and GLUT-1, markers of HIF pathway, are characteristic of ccpRCC, and ccRCC, while contrasting with papillary-RCC [19].

The transcription factor GATA-3, involved in cancer development, tumor differentiation, epithelial-mesenchymal transition, stains positive in about one third of ccpRCC and is emerging as a specific marker [26]. Stains for CD10, RCC antigen, α-methylacyl-CoA racemase (AMACR), transcription factor E3 (TFE3), and translocation factor EB (TFEB) are generally negative [4, 19].

Therefore, the ccpRCC immunohistochemical phenotype ($CK7^+$, CAIX+, $AMACR^-$, $34\beta E12^+$, CD10- $TFE3^-$) allows differentiating this tumor from other kidney cancer types with overlapping histomorphological features.

Molecular Features

Chromosomal Copy Number Alterations

Deletion of chromosome 3 and loss of the locus-specific subtelomeric chromosome 3p by fluorescence in situ hybridization [27] (and subsequent inactivation of several tumor suppressor genes, including *VHL, BAP1, PBRM1* and *SETD2*], which represent a critical event of ccRCC carcinogenesis is typically absent in ccpRCC [4, 24].

Copy number variations of chromosomes 7, 17 and Y, are distinctive features of papillary RCCs but are absent in ccpRCC [4, 6].

Although it is debated, several analyses reported different chromosomal aberrations in ccpRCC, including trisomy of chromosomes 10 and 12 [28], monosomy of chromosomes 16, 17, and 20 by FISH [29].

Gene Mutations

Characteristically, ccpRCC, unlike ccRCC hystotype, do not harbor von Hippel-Lindau (VHL) gene mutations or *VHL* gene promoter methylation [19, 26]. Quantitative RT-PCR analysis reveals normal or even elevated VHL mRNA expression in ccpRCC compared to non-neoplastic controls, although in absence of *VHL* inactivating mutations or chromosome 3p losses. This finding could suggest the existence of alternative molecular mechanism leading HIF pathway up-regulation independent from *VHL* gene mutations, being ccpRCC positive for HIF [19].

Tumors that histologically resemble ccpRCC (defined as ccpRCC-like tumors) may occur in patients with VHL disease, but generally present an immunohistochemical (diffuse CD10 staining, negative CK7 labeling, and strong AMACR reactivity) and molecular profile (loss of 3p in about 80% by FISH - similar to ccRCC -, no chromosomes 7 or 17 aberrations) diverse from sporadic ccpRCC, implying a different pathogenesis [7, 29].

Using targeted next-generation sequencing (NGS) technology to sequence several common tumor-associated mutation 'hot-spots' in ccpRCC, Lawrie and Colleagues firstly identified few somatic mutations in ccpRCC [30] as Raspollini et al. [31]. Interestingly, Lawrie et al. observed mutations as follows: 1) mutations within intronic regions close to splice junction (comprising mutation in *ERBB4, PTEN*, and *STK11* genes), whose functional significance is still unknown; 2) synonymous mutations, which do not directly modified the produced amino acid sequence; 3) non-synonymous mutations affecting the proto-oncogene *MET* (the T992I and N375S mutational variants) associated with epithelial-to-mesenchymal transition (EMT) [30]. Furthermore, the non-coding RNA expression analysis revealed a different expression of mature (entire miRnome), precursor (pre)-miRNAs, small nucleolar (sno)RNA and small Cajal body-specific (sca)RNAs between ccpRCC and ccRCC or papillary RCC subtypes [30]. Interestingly, and in contrast to other kidney cancer histotypes, the miRNA analysis showed the over-expression of all five members of the miR-200 family (miR-200a, miR200b, miR200c, miR-141, and miR-429 – regulators of EMT) in ccpRCC tumors, emphasizing the impaired (incomplete or blocked) process of EMT probably responsible for the indolent biological behavior of this entity [32].

The mRNA expression levels of eight genes typically altered in ccRCC and papillary RCC (*AMACR*, BMP and activin membrane-bound inhibitor homolog [*BAMBI*], *CAIX*, ceruloplasmin, nicotinamide N-methyltransferase [*NNMT*], schwannomin-interacting protein 1 [*SCHIP1*], solute carrier family 34 (sodium phosphate) member 2 [*SLC34A2*], and vimentin [*VIM*]) have been assessed by real-time (RT)-PCR among ccpRCC [30]. Although all eight genes were identified in ccpRCC, their levels of expression differed compared to other RCC histotypes. In particular, compared to papillary RCC, ccpRCC showed higher expression of *CAIX*, *CP*, *NNMT*, and *VIM*, lower *AMACR*, *BAMBI*, and *SLC34A2* expression, and comparable levels of *SCHIP1*. Compared with ccRCC, ccpRCC expressed marginally less *NNMT*, but similar levels of the other genes [27].

All aforementioned details are sum up in Table 1, Figs. 2 and 3.

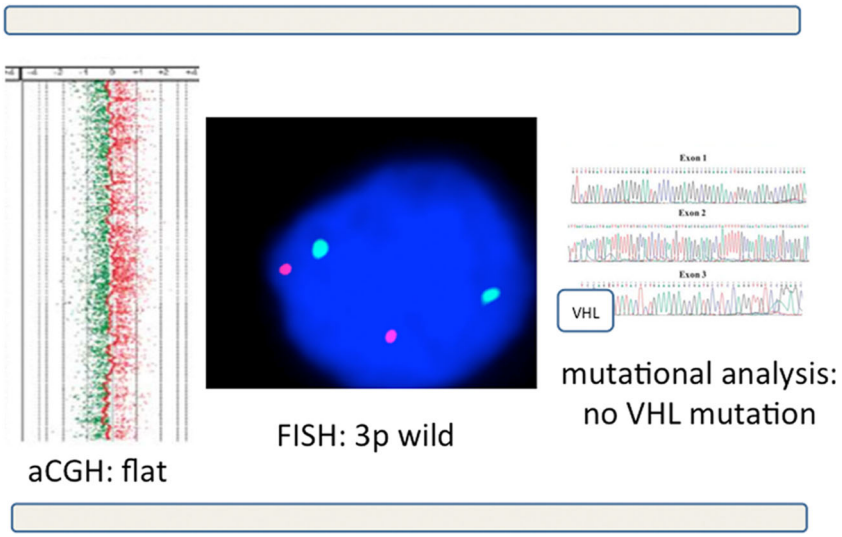

Fig. 2 Genomic profiling of clear cell-papillary RCCs. Flat aCGH wide genomic profile, absence of cytogenetic deletion of chromosome 3p and absence of VHL gene mutation

Differential Diagnosis

A correct diagnosis of ccpRCC is of crucial importance [33] for the therapeutic management, the timing of follow-up and the impact on patient's life. Three mainly relevant RCC tumor entities should be considered in the differential diagnosis: ccRCC, especially with low Fuhrman or low ISUP/WHO nucleolar grade, papillary RCC and multiocular cystic RCC with low malignant potential and rarely Xp11.2 translocation RCC. Clear cell RCCs, in contrast to ccpRCC, usually are positive for CD10, negative for CK7 and harbor *VHL* gene mutations/3p deletions.

The papillary architecture could raise problems in the differential diagnosis with papillary RCC. However, the clear cells are an uncommon finding in papillary RCCs. Moreover, the positive staining for AMACR, and the absence of reactivity for CAIX and HMWK in papillary RCCs help in challenging cases. Papillary RCCs (both type 1 and 2 subtypes) typically harbor genetic abnormalities such as trisomy of chromosomes 7 and 17, while type 2 papillary RCC

WHO 2016: the new clinico-pathological tumour entity called "clear cell-papillary RCC"

Nomenclature (WHO 2016 classification of renal neoplasia)

1) Names: clear-cell papillary RCC, clear cell (tubulo)papillary RCC, renal adenomatoid tumour (RAT)
2) Diagnostic recruitement: ex clear cell RCCs

Epidemiology and clinics

1) Incidence: from 2 to 9% of renal neoplasia
2) Clinical setting: sporadic, end-stage kidney, de novo tumours after kidney transplantation

Pathology

1) Morphology: tubulo-papillae lined by clear cell with nuclei aligned
2) Immunohistochemistry: CK7++, CAIX cup-like expression, CK34bE12+
3) Molecular profiling: VHL no mutation, flat profile at wide genomics

Oncology

1) Outcome: no recurrences or metastases, no lymph-nodal involvement
2) Overall biology assessment: behaviour as a clear cell renal cell adenoma, benign at clinics

Fig. 3 Sum up of clinico-pathological characters of clear cell-papillary RCCs accoridng to WHO 2016 classification

frequently carries the Y chromosome loss which are lacking in ccpRCC [6, 19, 34]. MiT family translocation RCCs are rule out by the absence of cathepsin-k immunoexpression.

Clear cell papillary RCC and RAT has actually to be differentiated from conventional clear cell RCC with abundant fibroleiomyomatous stroma [35–39] and from a more recent distinct genomic tumor called *TCEB1* mutated renal cell carcinoma [40].

Prognosis and Outcomes

All follow-up data and outcomes are summarized in Table 2 and Fig. 3.

Clear cell papillary RCC is characterized by an indolent clinical behavior, based on follow-up with a mean of 38 months reported (3,5 years) following 362 patients affected (see Table 2). In fact, no cases of local recurrence, lymph-node or distant metastases, and disease-related death have been described to date (see Table 2) irrespective of the clinic-pathological presentations (see Table 2). Moreover, the diagnosis of the vast majority of these tumors (small, well-circumscribed, unifocal masses) occurs in very early stage (stage I for almost all cases, rarely in stage II) (see Table 2). To further support the favorable clinical course related to ccpRCC, lympho-vascular invasions, tumor necrosis, and renal sinus infiltration - confirmed marks of negative prognostic value – have not been reported in association with ccpRCC. Recently, sarcomatoid transformation have been reported by Diolombi et al. [41]. Analogously to ccpRCC, RAT cases present a benign biological behavior, with no local/distant recurrence after surgery (see Table 2). The benign clinical course of ccpRCC/RAT tumors could biologically be justified by the activation of specific signaling pathways associated with good prognosis.

It is therefore not surprising that the debate on the most appropriate terminology to use for labeling this renal cancer subtype is still open. If the benign clinical behavior of this entity will be unequivocally confirmed, it would be conceivable to definitively abandon the misleading term of "carcinoma"? Carcinoma is an epithelial neoplastic lesion with the potential behavior to metastasize. Adenoma is an epithelial neoplastic lesion with absence of aforementioned capacity.

Up to date the term "clear cell papillary adenoma" could be replaced to these tumors as all reported evidenced benign appearance, no one tumor reported showed M1 staging along many years of follow-up, with no N1+ findings. It is not just mere semantics, but it would be of great importance especially 1) to reduce the patients psychological impact related to the diagnosis of a malignant neoplasia, 2) to avoid close and invasive follow-up, 3) to better guide therapeutic management of small renal tumors, 4) to avoid bias in the cohort of ccRCC used as control in studies focusing on prognostication, 5) to promote conservative surgery where possible or a conservative approach by active surveillance in high-risk surgical patients (single kidney or renal chronic failure patients).

Conclusion

The new tumor entity denominated "*clear cell-papillary renal cell carcinoma/RAT*" according to the WHO 2016 new classification, have the clinical characters of a renal cell adenoma as does harbor a benign outcome. The incidence range from 2 to 9% of consecutive renal cell neoplasia and the knowledge of aforementioned clinic-pathological information open new approaches (minimal surgical approach such as enucleation, active surveillance or minimal follow-up and appropriate identification with immunophenotypical and molecular analysis on tissue either whole tumour or biopsy) to patients affected by *clear cell-papillary renal cell carcinoma/RAT* neoplasms. Our review does highlight important information for oncologists such as the absence of any recurrence or any metastases for patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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