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EDITORIAL COMMENT

The World Health Organization 2022 Classification of renal tumors: key updates for urologists

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The latest classification of tumors of the urinary system and male genital organs released by the World Health Organization (WHO) in August 2022 highlighted the advancements in our understanding of renal tumors.[1-3]

Compared with the previous classifications,[4] in which a list of tumors was enumerated, the main novel aspect of the fifth edition is the introduction of subcategories defined on the basis of specific features, as follows: 1) clear-cell renal tumors; 2) papillary renal tumors; 3) oncocytic and chromophobe renal tumors; 4) collecting duct tumors; 5) other renal tumors; 6) molecularly defined renal carcinomas.[1, 2] The latter subgroup and the new molecular-driven histotypes introduced in the last WHO emphasize the role of molecular findings.

In this regard, we read with great interest the recent review by Moch *et al.* summarizing the most significant changes introduced by the 2022 WHO classification.[2] The Authors indeed pointed out the concept of molecularly defined renal tumors and how combined morphological features with molecular data may form an "integrated" diagnosis. As they stated, "*in the next years, massive parallel sequencing will be used more and more to identify molecular alterations in renal tumors with unusual morphology*"[2]. Although we do agree on the central role of molecular analysis in the biological comprehension of renal tumors, and their potential better definition in tertiary referral academic centers, the routine application of molecular techniques in daily clinical practice might be unsustainable. Nevertheless, pathologists should be able to recognize molecular entities such as fuma-

rate hydratase (FH) – deficient renal cell carcinomas[5] and succinate dehydrogenase (SDH) – deficient renal cell carcinoma.[6] Both tumors may arise as a solitary mass in the hereditary background due to germline mutation of the *FH* gene or any one of the *SDH* genes respectively. Instead of performing molecular analysis, loss of immunohistochemical stain of FH/SDH, as a surrogate of *FH/SDH* gene mutation, has been proven to be a valuable tool for screening. The proper identification of those tumors is mandatory not only for the patients to eventually identify other tumors and for prognosis (FH-deficient renal cell carcinoma displays an aggressive clinical course whereas SDH-deficient renal cell carcinoma has an indolent behavior) but also for their relatives to promote genetic counseling.[7]

Another important aspect underlined by the Authors, which we strongly support, is the active role of pathologists in designing new clinical trials.[2] Looking at the new WHO classification it is easy to see how pathologists and clinicians are "traveling" at two different speeds. While pathologists are introducing more and more entities (21 renal cell tumors so far[1, 2]), in clinical trials we still basically distinguish clear cell renal cell carcinoma (RCC) from non-clear cell RCC. Although we are aware of the difficulty of enrolling patients with less common hystotypes in clinical trials, we truly believe that the integration of morphological-based diagnosis with molecular features will be essential to reach precision oncology and personalized therapy.

The increasing complexity of the latest WHO classification is particularly evident for eosinophilic renal tumors, which could provide unique challenges for both clinicians and pathologists. Besides oncocytomas and chromophobe RCC, eosinophilic solid and cystic (ESC) RCC, low-grade oncocytic tumor (LOT) and eosinophilic vacuolated tumor (EVT) entities share morphological, molecular (*mTOR/TSC* genes alterations), and clinical features (low malignant potential).[2] Although the distinction is biologically relevant, in daily clinical practice their differential diagnosis might not infer any different management.[8, 9] Therefore, in the current WHO classification, they are designated as "oncocytic renal neoplasms of low malignant potential NOS." This concept is important for surgical specimens but particularly relevant for renal biopsy specimens. The differential diagnosis between *oncocytic renal neoplasms of low malignant potential vs.* other RCC hystotypes is likely to be reliable in high-volume centers with dedicated uropathologists (using routinely immunohistochemistry techniques), and may have clinically-significant implications during shared decision-making.[10-12]

On the other hand, this diagnosis should be feasible in different worldwide laboratories. For this reason, the latest edition of WHO promotes the use of this nomenclature (oncocytic renal neoplasms of low malignant potential) to provide an operative framework to assist clinicians and pathologists.

Such a pragmatic differential diagnosis would be valuable to optimize the selection of the best candidates for active surveillance *vs.* upfront intervention among patients with localized renal masses, after careful consideration of life expectancy, comorbidity burden, frailty and tumor-related characteristics.[9, 10, 13, 14]

Lastly, one of the key characteristics of a good classification system is the clinical relevance of the recognized histopathological entities.[15] In this perspective, the most relevant changes introduced by the new WHO classification on renal tumors that could impact clinical practice can be summarized as follows:

• the change in nomenclature from clear cell papillary RCC to clear cell papillary renal tumor, in light of the indolent behavior of this entity and no evidence of recurrence;[16] embracing this change by urologists will allow to tailor the follow-up strategy, avoiding unnecessary imaging and costs;[17]

• the subcategorization into type 1 and type 2 papillary RCC, which is no longer recommended based on the acknowledgment of several entities with different molecular backgrounds within type 2 papillary RCC;

• the identification of the FH-deficient and SDH-deficient RCC entities, that represents an important step toward personalized decision-making in patients with hereditary RCC;

• the recognition of ALK-rearranged RCC, which opens new horizons given the potential

effective treatment offered by targeted ALK inhibitors;

• the preferred term for renal angiomyolipoma (AML) is classic angiomyolipoma or PEComa (perivascular epithelioid cell tumor) of the kidney, with two AML subtypes (oncocytic AML and AML with epithelial cysts);

• the syndromes associated with kidney tumors include: BAP1 tumor predisposition syndrome, hyperparathyroidism-jaw tumor syndrome, FH-deficient RCC, Birt-Hogg-Dubé Syndrome, hereditary pRCC, Cowden Syndrome, SDH-deficient tumor syndromes, tuberous sclerosis, and von Hippel-Lindau Syndrome (type 1 and 2; type 2 is part of hereditary phaeochromocytoma-paraganglioma syndrome).

In conclusion, RCCs and other renal tumors include a broad spectrum of histopathological entities. The fifth edition of the WHO classification of renal tumors provides an update on these entities (including diagnostic criteria), molecular correlates, and an updated nomenclature.[1, 2, 18] Of note, this classification has been also implemented in the latest European Association of Urology (EAU) guidelines on renal cell carcinoma (RCC) (https://uroweb.org/guidelines/renal-cell-carcinoma).

Future research efforts should be focused on exploring the impact of the new WHO classification, aiming to provide patients and urologists the evidence needed to tailor clinical decisions according to the individual patient's and tumor's peculiarities.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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