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LETTER TO THE EDITOR

"Renal cell carcinoma, not otherwise specified" is not a sufficient diagnostic classification

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Received: 3 April 2026 / Revised: 9 June 2026 / Accepted: 23 July 2026
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Dear Editor,

Renal cell carcinoma, not otherwise specified (RCC, NOS) lacks defining features of any recognized and/or emerging renal neoplasms in the latest World Health Organization classification [1]. There is no strict diagnostic framework for RCC, NOS, therefore it represents a morphologically, immunohistochemically, and molecularly heterogeneous group of tumours [1–3]. With the addition of the new category of tumors known as the molecularly defined renal carcinomas (MDRC), molecular work-up, along with the other diagnostic assays such as comprehensive immunohistochemical (IHC) panel, is required before diagnosing RCC, NOS. Since the majority of the surgical pathology laboratories lack necessary IHC and/or molecular tools to sufficiently diagnose (or exclude) all identified renal neoplasms including MDRC, the diagnosis of RCC, NOS often labels tumours that may in fact be classifiable, but the necessary IHC or molecular workup is unavailable in the pathology laboratory and/or health care system. The term "RCC, NOS" alone, therefore, does not confer a clarifying diagnostic statement to the multidisciplinary cancer care team regarding the biology and the disease course.

The diagnostic designation of RCC, NOS reflects fundamentally different circumstances depending on whether the renal neoplasm is evaluated in a resource-limited pathology laboratory or a large referral center. Common scenarios for RCC, NOS may include renal tumors with clear cell cytology with true papillary formation or without CA9 expression; eosinophilic renal tumors without classical features of oncocytoma or chromophobe RCC or lack of KIT/KRT7 expression; or high-grade infiltrative kidney tumors. These morphological and immunophenotypical scenarios are frequent manifestations of MDRC [4], which cannot be definitively diagnosed in limited resource setting due to the lack of requisite molecular testing or other surrogate assays, such as SDHB IHC for succinate dehydrogenase deficient RCC. In these situations, a renal tumor with RCC, NOS diagnosis in a limited-resource setting may well be re-visited and the definitive RCC subtype can be diagnosed with adequate work up. Instead of solely labeling a tumor as RCC, NOS, a morphology-based sub-stratification of RCC, NOS as a diagnosis may restore the necessary communication between the surgical pathologist and other members of the clinical care team as well as the pathologists in the referral centers. In some cases, definitive subclassification may not change the patient's treatment yet can still alter clinical follow-up and prompt family screening, particularly when a tumor is reported under the proposed classification as a RCC, NOS with oncocytic/eosinophilic features. For example, low-grade oncocytic/eosinophilic tumors are usually indolent and surgical resection is generally curative, due to the potential for underlying germline alterations in genes such as FLCN or within the mTOR/TSC pathway, their recognition retains clinical importance beyond local tumor control [5, 6]. Such alterations may carry syndromic

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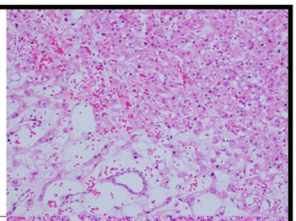
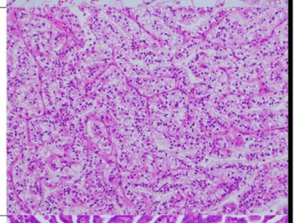
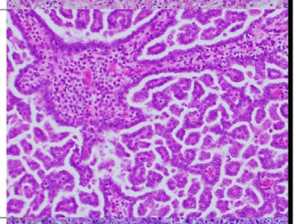
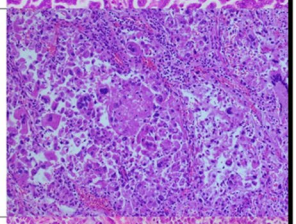
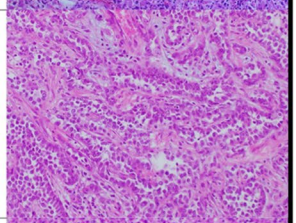
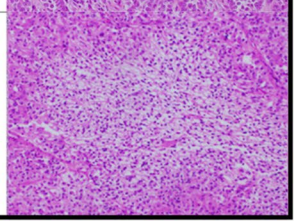
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Published online: 05 August 2026

implications that affect patient surveillance and family screening. While germline testing is most readily justified in younger patients, the broad age range of these tumors and the occurrence of the relevant alterations in both germline and somatic settings argue that this category should not be dismissed even when the index lesion is expected to behave indolently [6]. Herein, we propose a descriptive, morphology-based set of subgroups for reporting RCC NOS (Table 1)

Table 1 Proposed morphologic sub-classification framework for renal cell carcinoma, not otherwise specified (RCC, NOS). "(i)" suffix: when appended to RCC, NOS (i), this designation indicates that the diagnosis was rendered in a resource-limited setting in which one or more essential ancillary studies (e.g., immunohistochemistry and/or molecular testing) required for definitive subclassification were unavailable or not feasible. This suffix promotes transparency regarding diagnostic context without compromising morphologic reporting integrity. Mixed pattern: this category is reserved for tumors in which two or more distinct architectural and/or cytologic components are present in roughly comparable proportions, with no single dominant pattern; it does not refer to the minor, incidental focal heterogeneity common in renal tumors. Only the principal coexisting components should be listed, rather than every focal pattern

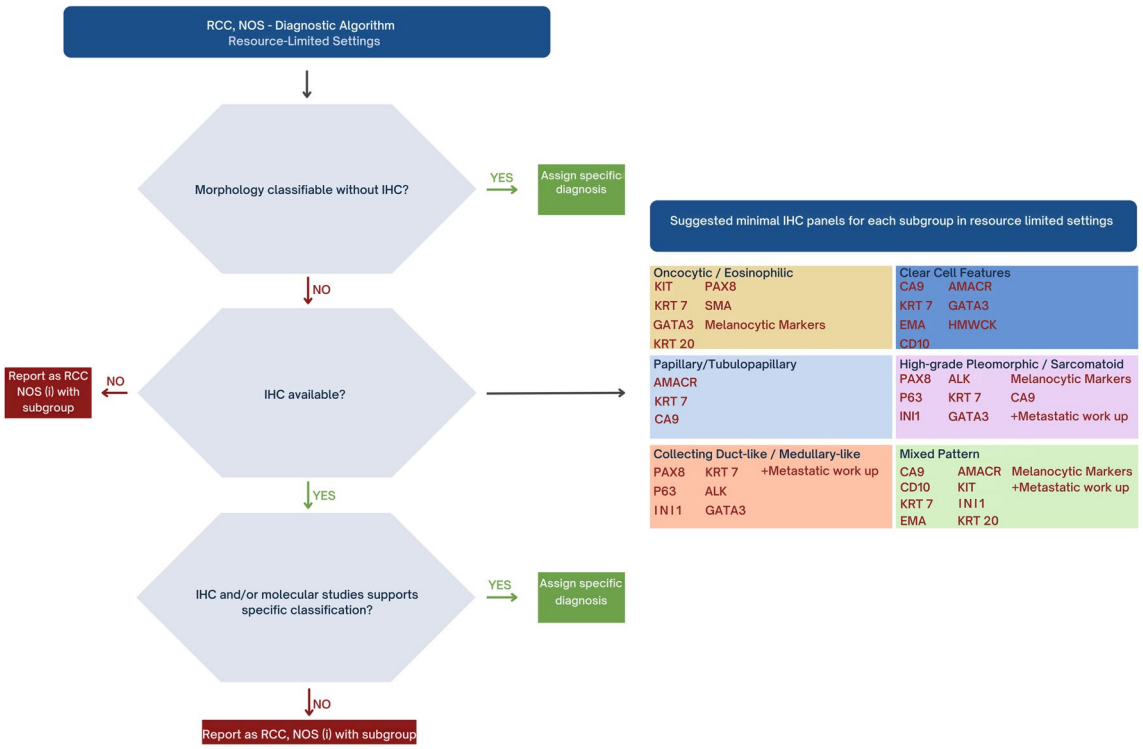
RCC, NOS Subgroup	Dominant Morphology	Key Differentials	Histopathology
RCC, NOS with Oncocytic/Eosinophilic Features	Solid, nested or tubulocystic growth with eosinophilic cytoplasm	Oncocytoma, low-grade oncocytic tumor, chromophobe RCC, SDH deficient RCC, emerging eosinophilic entities	
RCC, NOS with Clear Cell Features	Predominantly clear cytoplasm	Clear cell RCC variants, TFE3/TFEB-altered RCC, other clear cell-predominant tumors	
RCC, NOS with Papillary/Tubulopapillary Architecture	Papillary or tubulopapillary growth pattern	Papillary RCC, MiT family RCC, MTSCC, CCTPRT and other papillary-pattern tumors	
RCC, NOS with High-grade Pleomorphic/Sarcomatoid/ Dedifferentiated Features	Marked pleomorphism, sarcomatoid or rhabdoid change, extensive necrosis	Sarcomatoid transformation of known RCC subtypes, metastatic carcinoma, urothelial carcinoma, mesenchymal neoplasms	
RCC, NOS with Collecting Duct-like/Medullary-like Features (High-grade Infiltrative)	High-grade infiltrative carcinoma with desmoplasia and inflammation	Collecting duct carcinoma, renal medullary carcinoma, ALK RCC, urothelial carcinoma, metastasis	
RCC, NOS with Mixed Pattern	Distinct architectural/ cytologic components with estimated proportions	Composite or collision tumors, divergent differentiation, MiT family RCC	

Abbreviations: *RCC* renal cell carcinoma, *NOS* not otherwise specified, *SDH* succinate dehydrogenase, *MiT* microphthalmia transcription factor, *TFE3* transcription factor E3, *TFEB* transcription factor EB, *ALK* anaplastic lymphoma kinase, *MTSCC* Mucinous tubular and spindle cell carcinoma, *CCTPRT* Clear cell (tubulo)papillary renal cell tumor

to communicate the dominant patterns and the most relevant differentials. In addition to the dominant morphologic pattern, we recommend that each subgroup designation be reported together with adverse histologic features such as coagulative necrosis, desmoplasia and mitotic activity so as to convey risk stratification relevant to clinical management. Grading should, however, be applied in an entity-aware manner, as WHO/ISUP nuclear grade was developed for clear cell and papillary RCC and may be misleading in certain emerging entities, which often display prominent nucleoli suggestive of high grade yet typically behave indolently [7]. A diagnostic algorithm for RCC, NOS in resource-limited settings is provided in Table 2.

If RCC NOS is approached and reported using the proposed morphologic sub-stratification, it ceases to be a purely indeterminate diagnosis and instead becomes a structured, interpretable category. Historical cohorts labeled as "RCC NOS" represent profoundly heterogeneous populations, often combining indolent low-grade tumors, oncocytic neoplasms, clear cell-like lesions, and highly aggressive sarcomatoid carcinomas within a single analytic category, despite their markedly different biological behavior and prognosis [8, 9]. Any conclusions drawn from such mixed cohorts are therefore methodologically unstable and biologically difficult to interpret. Re-framing RCC, NOS as a set of reproducible morphologic subgroups allows future studies to be conducted within more biologically coherent categories, generating data that are more meaningful, comparable, and clinically actionable. In addition, such an approach may facilitate retrospective archival studies by enabling investigators to more efficiently identify candidate cases when newly defined tumor entities emerge, thereby accelerating reclassification and reducing the time required to recognize previously unclassified tumors.

Table 2 Proposed diagnostic algorithm for RCC, NOS in resource-limited settings. The term "melanocytic marker" denotes any of HMB45, melan A, or MITF, allowing flexibility in marker selection. Additional, less widely available markers, such as FH, cathepsin K and GPNMB, were not incorporated into the core panels given their limited availability in resource-limited settings but may contribute to the differential diagnosis where accessible (e.g., in MiT family translocation and TSC/MTOR-pathway–related RCC and FH-deficient RCC)



Abbreviations: *RCC* renal cell carcinoma, *NOS* not otherwise specified, *IHC* immunohistochemistry, *KIT* KIT proto-oncogene receptor tyrosine kinase, *KRT7* keratin 7, *KRT20* keratin 20, *PAX8* paired box gene 8, *SMA* smooth muscle actin, *HMB45* human melanoma black 45, *CA9* carbonic anhydrase IX, *AMACR* alpha-methylacyl-CoA racemase, *GATA3* GATA binding protein 3, *EMA* epithelial membrane antigen, *CD10* cluster of differentiation 10, *HMWCK* high-molecular-weight cytokeratin, *P63* tumor protein p63, *INI1* integrase interactor 1 (SMARCB1), *ALK* anaplastic lymphoma kinase, *Melan A* melanoma antigen A, *MITF* melanocyte inducing transcription factor, *FH* Fumarate hydratase, *GPNMB* glycoprotein nonmetastatic melanoma protein

Acknowledgements None.

Author contributions MA and NAY contributed to the conception and design of the study. NAY prepared the first draft of the manuscript. All authors contributed to manuscript revision, provided critical intellectual input, and approved the final version of the manuscript.

Funding The authors have no financial disclosures relevant to this work.

Data availability No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Declarations

Ethics approval According to institutional and national guidelines, formal ethics committee approval was not required.

Competing interests The authors declare that they have no competing interests.

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