Advancing Care in Non-Clear Cell RCC: Optimizing ICI and TKIs

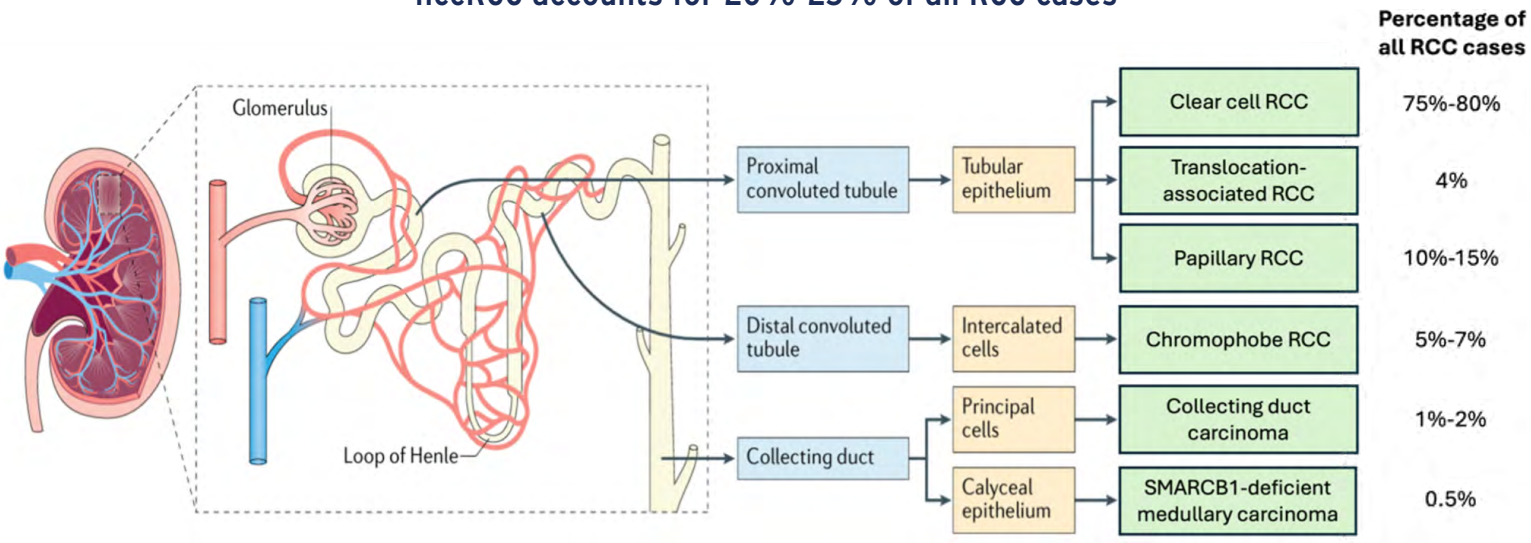
Complexities in the Diagnosis of nccRCC: How Can We Do Better?

Learning Objectives

- Recall the importance of accurate diagnosis and classification of non–clear cell renal cell carcinoma (nccRCC)
- Demonstrate increased knowledge of nccRCC subtypes, molecular mechanisms, and prevalence

Renal cell carcinoma (RCC) can be classified by histologic or molecular subtype[1-3]

nccRCC accounts for 20%-25% of all RCC cases[2]



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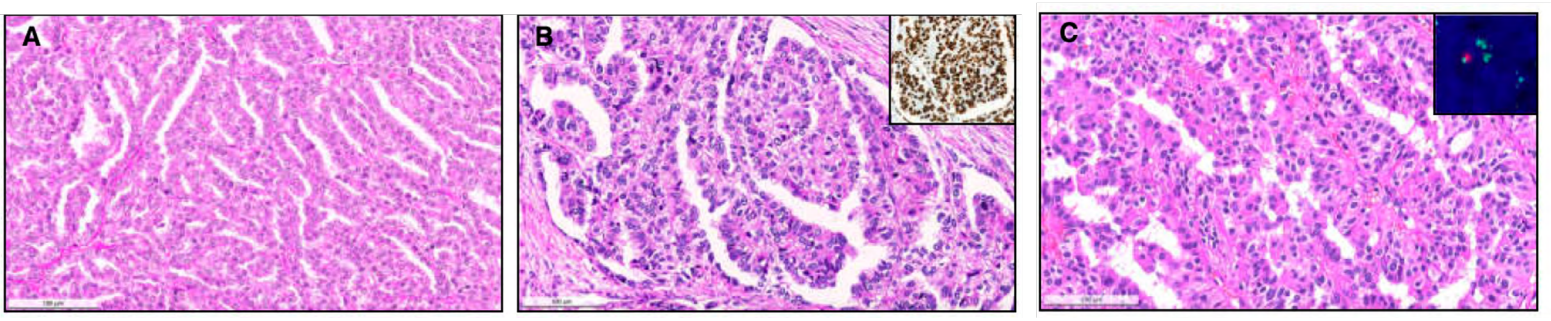
Papillary tumors represent the largest nccRCC subtype, have heterogeneous morphology, and may coalesce with some new molecular subgroups[4, 5]

Classical papillary RCC | TFE3-rearranged RCC | *TFEB*-amplified RCC



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The WHO 2022 classification of urogenital tumors introduced subgroups of molecular-driven, morphologically heterogeneous RCC[3]

RCC Subtype	Genetic Alteration	Comments
Eosinophilic solid and cystic RCC	*TSC* mutation Activation of mTOR pathway	Typically clinically indolent Appears responsive to mTOR inhibitors
ALK-rearranged RCC	*ALK* rearrangements	Typically morphologically heterogeneous Appears responsive to ALK inhibitors
SMARCB1-deficient medullary carcinoma	*SMARCB1* loss	Highly aggressive Generally occurs in young patients with sickle cell trait
TFEB-altered RCC	*TFEB* translocation TFEB amplification	*TFEB*-translocated: typically clinically indolent TFEB-amplified: typically highly aggressive, tends to occur in older patients Formerly categorized as MIT family RCC
TFE3-rearranged RCC	*TFE3* translocation	Formerly categorized as MIT family RCC
FH-deficient RCC	*FH* loss or mutation	Formerly termed HLRCC

ALK, anaplastic lymphoma kinase; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; MIT, microphthalmia; mTOR, mammalian target of rapamycin; SMARCB1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; TFE3, transcription factor binding to IGHM enhancer 3; TFEB, transcription factor EB; TSC, tuberous sclerosis complex.

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