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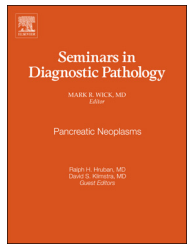

The evolving classification of renal cell neoplasia

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ABSTRACT

The classification of renal cell neoplasia is morphologically based; however, this has evolved over the last 35 years with the incorporation of genetic characteristics into the diagnostic features of some tumors. The 2013 Vancouver classification recognized 17 morphotypes of renal parenchymal malignancy and two benign tumors. This classification included the newly established entities tubulocystic renal cell carcinoma (RCC)), acquired cystic disease-associated RCC, clear cell (tubulo) papillary RCC, microphthalmia transcription factor family translocation RCC and hereditary leiomyomatosis RCC syndrome-associated RCC. In addition to these newly described forms of RCC there are a number of novel tumors that are currently recognized as emerging entities. These are likely to be incorporated into subsequent classifications and include thyroid-like follicular RCC, succinate dehydrogenase B mutation-associated RCC, ALK translocation RCC, tuberous sclerosis complex-associated RCC, and RCC with (angio) leiomyomatous stroma.

Renal cell neoplasms are tumors derived from the epithelial components of the nephron and are the most commonly encountered tumors of the upper urinary tract. Although the earliest confirmed case of renal carcinoma was reported over 200 years ago,[1] it is only over the past 30 years that our understanding is that renal cell tumors represent a morphologic spectrum of tumors that differ in architecture, genetics, and clinical behavior has developed.[2]

Prior to 1835, reports of renal malignancy appeared as single case studies. During this period, 20 individual tumors were reported, although a number of these appear, on review, to be metastases from extra-renal primary malignancies. In his *Treatise on Renal Diseases* published in three volumes between 1837 and 1841, Rayer[3] detailed 13 further renal tumors and devised a classification based upon the gross description of the tumor and associated clinical findings. Prior to this, renal malignancy had been classified by Koenig in 1826 on the basis of gross morphology as scirrhous, steatomatous, fungoid, and medullary tumors[1] and later by Cornil and Ranvier[4] as scirrhous, encephaloid, hematoid, colloid, and melanotic.

In early studies on renal neoplasia, there was widespread acceptance that these tumors were of renal tubule origin. This was first proposed by Robin in 1855 and was supported by the observations of Waldeyer, who in 1867 described the tumor as being derived from renal tubular epithelium.[1] Progress in our understanding of the pathogenesis of renal cell tumors was severely hampered by the theories of Grawitz[5,6] published in 1883 and 1884. The details of the hypernephroma controversy have been discussed previously,[1] but briefly, Grawitz postulated that small renal subcapsular renal tumors were derived from adrenal rests.

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Table 1 – World Health Organization histological classifications of renal cell neoplasia.

1981
Adenoma
Carcinoma
Renal cell carcinoma
Others
1998[14]
Benign—adenoma
Papillary/tubulopapillary adenoma
Oncocytic adenoma (oncocytoma)
Metanephric adenoma
Malignant—carcinoma
Renal cell carcinoma
Clear cell carcinoma
Granular cell carcinoma
Chromophobe cell carcinoma
Spindle cell carcinoma
Cyst-associated renal cell carcinoma
Renal cell carcinoma originating in a cyst
Cystic renal cell carcinoma
Papillary renal cell carcinoma
Collecting duct carcinoma
2004[17]
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

Table 2 – The Mainz Classification of Renal Cell Carcinoma.

Clear cell carcinoma	Basic
(proximal tubule)	Eosinophilic/granular
Chromophilic cell carcinoma	Basic
(proximal tubule)	Eosinophilic/granular
Chromophobe cell carcinoma	Basic
(connecting tubule)	Eosinophilic/granular
Duct Bellini carcinoma	Basic
(cortically medullary collecting duct)	Eosinophilic/granular

This theory was an expansion of the observations of Thornton, who in 1882 noted that an alveolar sarcoma of the capsule resembled the morphology of the adrenal gland. In 1884, Grawitz[6] expanded his conclusions and suggested that small alveolar tumors were of adrenal rest origin, while papillary tumors were primary renal malignancies. Despite this, there was a growing acceptance that all renal malignancies were of adrenal rest origin, being designated Grawitz tumors or hypernephromas.

Although the prevailing concept is that renal tumors are of adrenal tissue origin, detailed observations by Sudeck (1893) and Kelynak (1989) provided contradictory evidence. This was expanded by Stoerk in 1908, who concluded that hypernephroma and renal adenocarcinoma were indistinguishable and that all forms of hypernephroma were in reality varieties of a single tumor type. Increasing evidence as to the renal origin of renal cell tumors was provided by Zehbe (1910), Glynn (1912), Derrick (1922), Wright (1922), Newcomb (1936), and Willis (1948).[1] The true origin of renal cell neoplasia was conclusively determined by Oberling[7] in 1959, who showed that the ultrastructural features of these tumors were similar to those of renal convoluted tubule epithelial cells.

Early histological classifications of renal cell neoplasia varied in their complexity and were largely descriptive, recognizing that these tumors showed either a papillary or an alveolar morphology. The clarification by Oberling, as to the tissue of origin for renal cell tumors, provided an impetus for recognition that these tumors exhibit a variety of morphotypes. Papillary renal cell carcinoma (RCC) was reported as a distinctive tumor type by Manilla-Jimenez[8] in 1976, while collecting duct carcinoma had been earlier described in a single case report in 1949.[9] Renal oncocytoma was first described by Zippel[10] in 1942. Subsequent to this, occasional malignant oncocytomas were reported; however, the observation that some varieties of human renal carcinoma with eosinophilic and/or granular cytoplasm resembled a form of renal neoplasia induced experimentally in rats by nitrosomorpholine, led to the identification of chromophobe RCC by Thoenes in 1985.[11] Despite these advances, the 1981 WHO Renal Tumor Classification failed to fully recognize the various benign and malignant morphotypes of renal cell neoplasia that had been reported to date[12] (Table 1).

In a landmark work, Thoenes et al. classified the various RCC morphotypes that were then known and related these to tissues of origin within the nephron. It was also noted that each of the morphotypes of RCC could have eosinophilic and spindle cell/pleomorphic variants, and the resulting Mainz classification[13] (Table 2) gained considerable support in the prevailing literature.

The conference to formulate the second WHO Renal Tumor Classification was convened in Hamburg in 1989, with the publication delayed until 1998.[14] This classification adopted some of the features of the Mainz Classification but failed to recognize that neither granular cell nor spindle cell RCC is a distinctive morphotype of RCC (Table 1). The failure of the 1989/98 Classification to reflect the current understanding in the pathogenesis of RCC highlighted the need for a consensus meeting to provide a contemporary classification for RCC. In response to this, two meetings were convened independently to facilitate this task. The first of these was held in Heidelberg in 1996,[15] and the second in Rochester, Minnesota, in 1997. Although the Heidelberg meeting focused upon the genetic characterization of renal tumors, the one in Rochester was focused upon morphology,[16] the resulting classifications were almost identical and are now known collectively as the Heidelberg/Rochester Classification (Table 3).

The Heidelberg/Rochester Classification was expanded by the third WHO Renal Tumor Classification that was formulated in Lyon in December 2002. In this classification, the four main tumor morphotypes of the Mainz Classification [clear cell RCC, papillary (chromophilic) RCC, chromophobe RCC,