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Pathology and Molecular Pathogenesis of Renal Cell Carcinoma

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Abstract

Objectives: In this review, we summarise the World Health Organization (WHO) classification of renal cell carcinomas (RCCs) alongside grading and staging systems. General applications of immunohistochemistry, cytogenetics, and cDNA microarrays were reviewed with their implications in tumour diagnosis, prognosis, and therapy.
Results: RCCs are classified according to the 2004 WHO classification, which defines three main histopathologic tumour subtypes with distinct clinical behaviour and underlying genetic defects: conventional (clear cell), papillary, and chromophobe RCC. Histopathologic classification and specific genetic mutations are crucial in distinguishing between familial and nonfamilial tumours. The most common four-tiered Fuhrman nuclear grade system is recommended for all types of RCC. Tumour grade is assigned according to the highest grade present; staging is assigned using the Union Internationale Contre le Cancer/American Joint Committee on Cancer 2002 classification.
Conclusions: Prognosis of patients with RCCs is most accurately predicted by TNM stage. Within stages, Fuhrman grade has a strong predictive value. Although not considered in nuclear grading, sarcomatoid dedifferentiation is a severely negative event for all RCC subtypes. Histologic subtypes of RCCs are not independent prognostic factors comparable with TNM stage and Fuhrman grade. Histologic coagulative tumour necrosis was an independent prognostic factor of outcome for clear cell and chromophobe RCC. Immunohistochemical panels including RCC marker, CD10, and KIT are now available for differential diagnosis of the distinct RCC subtypes. Genetic studies have improved understanding of subtypes, offering a promising approach for clinical diagnosis, prognosis, and possibly therapy. Urologists should be aware that currently many molecular analyses can be performed on RCCs, and when feasible, fresh samples sent to the pathologist.

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1. Introduction

Renal cell carcinomas (RCCs) arise from the renal epithelium and account for >90% of all renal malignancies occurring in adult men and women. About 2% of RCCs are associated with inherited syndromes; specific oncogenes or tumour suppressor genes and their mutations have been identified for most of these (Table 1). Distinct genetic defects have also been described in nonfamilial RCC (Table 2). The Heidelberg classification, which was introduced in 1997 [1], described the identified genetic defects of both sporadic and familial RCC in relation to histopathologic appearance. The 2004 World Health Organization (WHO) classification [2] distinguishes three main histologic subtypes: conventional (clear cell), papillary, and chromophobe RCC. Rarer subtypes include carcinoma of the collecting duct of Bellini and new diagnostic categories as medullary carcinoma, Xp11 carcinoma, carcinoma associated with neuroblastoma (in long-term survivors of childood neuroblastoma), and mucinous tubular and spindle cell carcinoma. In a recent paper [3], these rare new entities have been duly revised, confirming that recognition of these tumours may have important implications for the patient's management. Additionally, ''RCC, unclassified'' was introduced as a novel diagnostic category to accommodate tumours that do not fit into any of the other morphologic categories. Representative examples of clear cell, papillary, and chromophobe RCC are shown in Fig. 1.

Table 2 – Genetic defects in nonfamilial renal cell carcinoma

Histotype	Chromosomes	Alterations
CCRCC	3	Deletions, mutations
PRCC	7 and 17	Trisomy and tetrasomy
Chromophobe RCC	1, 2, 6, 10, 13, 17, 21	Chromosomal loss

CCRCC = clear cell renal cell carcinoma; PRCC = papillary renal cell carcinoma.

2. Clear cell RCC

Clear cell RCC, which is the most common histologic variant, is a malignant tumour composed of cells with clear or eosinophilic cytoplasm. It usually presents as a solitary cortical tumour, and it occurs with equal frequency in either kidney. Multicentricity or bilaterality and early stage at the diagnosis are typical of inherited syndromes such as von Hippel-Lindau syndrome. Macroscopically, clear cell RCCs are round tumours that bulge out of the renal cortex. They are usually clearly demarcated from the adjacent renal parenchyma with a ''pushing'' border. All clear cell RCCs have a characteristic golden yellow appearance due to the rich lipid content of their cells. Cysts, hemorrhages, and calcifications are commonly encoutered. Tumour necrosis can also be present and should be routinely reported because it is a useful predictor of clinical outcome [4]. Microscopically, clear cell RCCs can present alveolar, acinar, or solid architectural patterns. A delicate vascular network of thin blood vessels is usually present. The cytoplasm of the neoplastic cells is usually clear, due to its lipid and glycogen content. A variable component of eosinophilic cells may be present. Nuclei are round to polygonal with indistinct nucleoli and finely distributed chromatin. Nuclear pleomorphism, prominent nucleoli, and coarse chromatin are typical features of high-grade tumours.

2.1. *Immunoprofile*

Clear cell RCCs commonly react with epithelial membrane antigen (EMA), low-molecular-weight cytokeratins (CK8, CK18, CK19), AE1, Cam 5.2, and vimentin. High-molecular-weight cytokeratins are rarely detected. MUC-1 and MUC-3 are consistently

Table 1 – Inherited renal cell carcinoma syndromes and related genetics defects

Syndrome	Gene	Chromosome alterations	Pathologic appearence
von Hoppel-Lindau	*VHL*	3p25 loss of function mutations	Multiple, bilateral CCRCC, phaeochromocytoma, CNS haemangioblastomas
Hereditary papillary renal carcinoma (HPRC)	*MET*	7q31 activating mutations	Multiple, bilateral PRCC, type 1
Hereditary leiomyomatosis and RCC	*FH*	1q42-43 inactivating mutations	Papillary renal cell carcinoma, non-type 1, cutaneous and uterine leiomyomas
Birt-Hogg-Dubè	*BDH*	17p11.2 inactivating mutations	Multiple chromophobe and clear cell RCC and oncocytomas, skin tumours
Familial clear cell renal cancer (FCCRC)		3p translocations	Multiple, bilateral CCRCC

CCRCC = clear cell renal cell carcinoma; CNS = central nervous system; PRCC = papillary renal cell carcinoma.