

EDITORIAL

THE HEIDELBERG CLASSIFICATION OF RENAL CELL TUMOURS

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SUMMARY

This paper presents the conclusions of a workshop entitled 'Impact of Molecular Genetics on the Classification of Renal Cell Tumours', which was held in Heidelberg in October 1996. The focus on 'renal cell tumours' excludes any discussion of Wilms' tumour and its variants, or of tumours metastatic to the kidneys. The proposed classification subdivides renal cell tumours into benign and malignant parenchymal neoplasms and, where possible, limits each subcategory to the most commonly documented genetic abnormalities. Benign tumours are subclassified into metanephric adenoma and adenofibroma, papillary renal cell adenoma, and renal oncocytoma. Malignant tumours are subclassified into common or conventional renal cell carcinoma; papillary renal cell carcinoma; chromophobe renal cell carcinoma; collecting duct carcinoma, with medullary carcinoma of the kidney; and renal cell carcinoma, unclassified. This classification is based on current genetic knowledge, correlates with recognizable histological findings, and is applicable to routine diagnostic practice. © 1997 John Wiley & Sons, Ltd.

*J. Pathol.* **183**: 131–133, 1997.

No. of Figures 0. No. of Tables 0. No. of References 16.

KEY WORDS—kidney; renal cell neoplasms; classification; genetics

INTRODUCTION

Classification systems at any given time reflect our technical abilities in the analysis of tumours and our actual theories on tumour development. In the past decades, the classification of renal cell tumours has been based on cytomorphological characteristics and presumed cellular origin, comparing the tumour cell phenotypes with mature counterparts in the renal

tubular system.<sup>1</sup> Recent advances in our understanding of the genetics underlying the pathogenesis of renal cell neoplasms have led to the recognition of distinctive types of tumours.<sup>2</sup> Our current understanding of tumour biology is that genetic alterations, transmitted during cell division, are fundamentally involved in neoplastic transformation. These genetic alterations affect the biology of the tumour cells, in respect of proliferation, cell death, differentiation, and cell adhesion; these very properties play a role in determining both the morphology and the behaviour of tumours. A histopathological classification of tumours which is based on a sound understanding of the genetic abnormalities involved will be robust in terms of biology, clinical behaviour, and response to therapy. However,

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Contract grant sponsors: Deutsche Forschungsgemeinschaft; Else Kröner-Fresenius-Stiftung.

any classification seeking to achieve general acceptance must also be based on morphological criteria which can be readily recognized in routine histological specimens. We believe that it is now possible to propose a histological classification of renal cell neoplasms which can be applied in every surgical pathology laboratory and yet which is based soundly on the genetic lesions which underlie the formation of the tumours in question.

### BENIGN PARENCHYMAL NEOPLASMS

*Metanephric adenoma* and *metanephric adenofibroma* are rare neoplasms composed of tubular or tubulopapillary structures and glomeruloid bodies of small cuboidal cells, reminiscent of embryonal metanephric tissue.<sup>3,4</sup> The term 'metanephric adenoma' is not ideal, because all primary neoplasms of the human kidney are metanephric in origin, but it has achieved widespread acceptance. The mixed adenomatous and stromal tumour originally designated as 'nephrogenic adenofibroma' seems to be closely related, and we suggest that this term be replaced with 'metanephric adenofibroma'. The genetics of metanephric adenoma and adenofibroma is not yet known.

*Papillary renal cell adenoma* has been described as having a combination of genetic alterations including trisomy of chromosomes 7 and 17 and loss of the Y chromosome.<sup>5</sup> Most of these tumours are incidental findings discovered at autopsy, or accompanying papillary RCCs in surgical specimens. Autopsy studies have shown that papillary renal cell adenomas are more common than all the other renal cell tumours combined.<sup>6</sup> The great majority of these tumours are composed of small 'blue' cells, or sometimes large eosinophilic cells showing solid-tubular-papillary structures. Psammoma bodies are frequent. In some cases, glomeruloid bodies may be seen. Combinations of genetic and clinicopathological analyses have suggested that it is not the size but the genetic alterations that determine the behaviour of these tumours.<sup>2</sup>

*Renal oncocytoma* comprises about 3–5 per cent of renal cell neoplasms in surgical series. These tumours are composed of cells with abundant eosinophilic cytoplasm filled with mitochondria. Usually they show an acinar growth pattern, but solid, trabecular, or even cystic growth may occur. The genetic changes include loss of chromosome arms 1p, 14q and loss of the Y chromosome or translocation between chromosome arm 11q13 and other chromosomes in a subset of tumours.<sup>7,8</sup> Many oncocytomas have an apparently normal karyotype.<sup>2</sup>

### MALIGNANT PARENCHYMAL NEOPLASMS

*Common or conventional renal cell carcinoma* accounts for about 75 per cent of renal cell neoplasms in surgical series. This type of renal tumour was separated from others based on the occurrence of a highly specific deletion of chromosome 3p.<sup>9</sup> Mutation of the VHL gene occurs exclusively in this type of renal tumour.<sup>10</sup> Dupli-

cation of chromosome band 5q22 and deletion of chromosome arms 6q, 8p, 9p, and 14q are characteristic alterations.<sup>2</sup> Recent studies have shown a significant association between loss of chromosome 14q segments and progression of this type of tumour.<sup>11</sup> The majority of common RCCs are composed predominantly of cells with clear cytoplasm in routine sections, although foci in which the cells have eosinophilic cytoplasm are common and may predominate. The growth pattern may be solid, trabecular, tubular, and cystic, although focal areas of papillary growth may be seen.

At the meeting, the best name for this tumour was a subject of controversy. Clear cell carcinoma is a widely used diagnosis in cytomorphologically oriented classifications and it is associated with a group of tumours which includes distinct genetic entities.<sup>2</sup> Confusion might therefore arise by using the same name for a genetically defined tumour. The term common or conventional renal cell carcinoma was preferred.

*Papillary renal cell carcinoma* accounts for approximately 10 per cent of renal cell tumours in surgical series. Trisomy of chromosomes 3q, 7, 8, 12, 16, 17, and 20 and loss of the Y chromosome are the most consistent genetic alterations.<sup>5</sup> The cells comprising these tumours may be small, with scanty cytoplasm, but they often have moderate to abundant cytoplasm with basophilic, eosinophilic or pale staining characteristics. Because of the variable affinity of the cytoplasm for routine stains, the term chromophil for this tumour type was not favoured by the majority of participants. A papillary growth pattern predominates in almost all of these tumours, although tubulopapillary and solid architecture may be seen. The development of papillary RCCs is associated with multiple bilateral microscopic lesions and papillary renal cell adenomas.<sup>9</sup>

*Chromophobe renal cell carcinoma* accounts for approximately 5 per cent of renal cell neoplasms in surgical series. Usually these tumours grow in large solid sheets and the cells have characteristic pale or eosinophilic granular cytoplasm, corresponding to a variable number of cytoplasmic microvesicles seen by electron microscopy. Hale's colloidal iron stain is helpful in the diagnosis.<sup>13</sup> Genetically, chromophobe renal cell carcinoma is characterized by a combination of loss of heterozygosity at chromosomes 1, 2, 6, 10, 13, 17, and 21 and hypodiploid DNA content revealed frequently by flow cytometric analysis.<sup>14,15</sup>

*Collecting duct carcinoma* accounts for approximately 1 per cent of renal cell neoplasms in surgical series and is a term which has been applied to carcinomas with differing appearances. The morphological features that are generally accepted are characterized by irregular channels lined by highly atypical epithelium which sometimes has a hobnail appearance. The channels are set in an inflamed desmoplastic stroma.<sup>16</sup> This appearance merges with that of a recently recognized variant of collecting duct carcinoma, *medullary carcinoma of the kidney*, which is believed to arise from the collecting ducts of the renal medulla and is associated with sickle cell trait. An affinity for the *Ulex europaeus* lectin supports a collecting duct origin in cases of renal cell carcinoma. Focal mucin production may be seen. No

consistent pattern of genetic abnormalities has been established.

*Renal cell carcinoma, unclassified* is a diagnostic category to which renal carcinomas should be assigned when they do not fit into one of the other categories, even after genetic analysis. In some surgical series, this group has amounted to approximately 3–5 per cent of cases. Since this category must contain tumours with a variety of appearances and genetic lesions, it is not susceptible to a limiting definition. However, examples of features which might prompt the assignment of a carcinoma to this category include apparent composites of recognized types, sarcomatoid morphology without recognizable epithelial elements, mucin production, mixtures of epithelial and stromal elements, and unrecognizable cell types.

It is recognized that *sarcomatoid change* has been found to arise in all types of renal cell carcinoma in this classification. Sarcomatoid features thus do not constitute a type *per se*, but rather are an indication of progression in renal cell carcinoma. Molecular analysis may help to assign a sarcomatoid renal cell carcinoma to a specific category when no epithelial areas are detected.

With these principles and classification in mind, the diagnosis of 'granular cell renal carcinoma', which has been used in the past, is no longer useful. Over the past two decades, oncocytoma and subsets of chromophobe renal cell carcinoma, papillary renal cell adenoma and carcinoma, and collecting duct carcinoma have been extracted from this heterogeneous group of tumours.

Although carcinoid tumours and small cell carcinomas rarely arise in the renal parenchyma, it is uncertain whether they arise from cells of the renal tubule and so they are not included in this classification of renal cell neoplasms.

We believe that this proposal, based on current genetic knowledge, correlates well with recognizable histological findings and is applicable to daily clinical

practice. We also believe that this classification has many advantages over previously proposed cytomorphologically based classifications.

### ACKNOWLEDGEMENTS

The workshop was supported by the Deutsche Forschungsgemeinschaft and Else Kröner-Fresenius-Stiftung.

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