7. Orditurs M, De Vita F, Catalano S. *Adult Wilms' tumor.* Cancer 1997; 80:1961-1965.
8. Davis CJ, Barton JH, Sesterhenn IA et al. *Metanephric adenoma. Clinicopathological study of fiftypatients.* Am J Surg Pathol 1995; 19:1101-1114.
9. Hannigar RA, Beckwith JB. *Nephrogenic adenofibroma: A novel kidney tumor ofyoung people.* Am J Sur9 Pathol 1992; 16: 325-334.
10. Mascarello JT, Cajulis TR, Krous HF et al. *Presence or absence of trisomia 11 is correlated with histologic subtype in congenital mesoblastic nephroma.* Cancer Cenet Cytogenet 1994; 77: 50-54.
11. Durham JR, Boatwick DC, Farrom GM at al. *Mesoblastic nephroma of adulthood. Report of three cases.* Am J Surg Pathol 1993; 17: 1029-1038.
12. Pawada J, Soosay SN, Deiprado W at al. *Cystic Hamartoma of the renal pelvis.* Am J Surg Pathol 1993; 17: 1169-1175.
13. Delahunt B, Beckwith JB, Eble JN at al. *Cystic embryonal sarcoma of kidney* Cancer 1998; 82: 2427-2433.
14. Truong LD, Williams R, Ngo Tat al. *Adult mesoblastic nephroma. Expansion of the morphologic spectrum and review ofliterature.* Am J Surg Pathol 1998; 22: 827-839.
15. Fans P, Argani P, Epstein JI at al. *Primany synovial sarcoma of the kidney: A molecular reappraisal of a subset of so-called embryonal renal sarcoma.* United States and Canadian Academy of Pathology, Annual Meeting, San Francisco, March 20-26, 1999.
16. Joshi VV, Beckmith JB. *Multilocular cyst of the kidney (cystic nephroma) and cystic, partially differentiated nephroblastoma. Terminology and criteria for diagnosis.* Cancer 1989; 64: 466-479.
17. Eble JN, Bonsib SM. *Extensively cystic renal neoplasms: Cystic nephroma, cystic partially differentiated nephroblastoma, multilocular cystic renal cell carcinoma, and cystic hamartoma of renal pelvis.* Samin Disgn Pathol 1998; 15: 2-20.

Clear renal cell carcinoma: Present status and grading

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It is now widely accepted that renal parenchymal carcinoma or renal cell carcinoma (RCC) is not a single tumor type but is a variety of tumors that can be classified according to morphology and genotype. The current understanding of the behavior of RCC largely relies on the results of reported series. In most of these series, all types of RCC were treated as a single tumor type rather than being subclassified according to morphotype.

Classification

Renal cell tumors dtsplay a heterogeneous morphology and their phenotype may change during progression. Thus, they may also change their pattern of differentiation during their life span and they do not necessarily retain the phenotype of their supposed progenitor cell. In addition, RCCs may be composed of admixtures of clear, granular or Chromophilic and spindle-shaped cells. These findings suggest that a transition between different phenotypes takes place during progression and, therefore, the cell type could not be used as an adequate parameter for accurate diagnosis. Advances in the understanding of the genetics underlying the development of renal cell neoplasms have led to the recognition of distinctive types of tumor. In fact, genetic alterations, transmitted during cell division, play a role in determining both the morphology and the behavior of tumors. For instance, most cytogenetic studies of clear cell carcinoma have found that loss of genetic material in the short arm of chromosome 3 (3p) is the most frequent and consistent abnormality. This means that a histopathological classification of RCC, which is based on the genetic abnormalities involved, is robust in terms of biology, clinical behavior and response to therapy. A classification based on morphology and in line with genetic facts as they are presently understood as well as being in line with the evolution of the neoplasms was proposed at the conference entitled Diagnosis and Prognosis of Renal Cell Carcinoma", held in Rochester, Minnesota, in March 1997. The renal cell neoplasms were divided into benign and malignant. The latter group of neoplasms included conventional (clear cell) renal carcinoma, papillary renal carcinoma, chromophobe renal carcinoma, collecting duct carcinoma and unclassified RCC.

Prognostic markers

Numerous parameters have been evaluated as prognostic markers for RCC with conflicting results. At present, only tumor stage has gained widespread acceptance among pathologists and urologists as an indicator of patient outcome. Of the other prognostic parameters tested in various prospective and retrospective studies, only assessment of tumor proliferation markers has shown a consist association with survival. Tumor angiogenesis, nuclear morphometry, tumor suppressor genes and growth factor expression have been correlated with survival for patients with RCC.

Tumor grade

Various grading systems have been proposed for RCC. Most of these have shown some degree of correlation with survival. Nuclear grading systems are the most widely used. The available evidence in the literature suggests that nuclear grading is a better prognostic indicator than other types that do not use nuclear criteria. Nuclear grading has prognostic value for conventional (clear Cell) and papillary RCC. There are two major problems with the proposed grading systems. The first is that the degree of correlation of the various systems with survival is not satisfactory. The other is the lack of observer consistency in assigning grading to RCC. The poor reproducibility of grading systems for RCC relates to the fact that the morphological changes are evaluated subjectively by the pathologist. An inference network, or Bayesian Belief Network (BBN), was developed by Dr Peter W. Hamilton (Belfast, UK) on the basis of previous experience acquired in the evaluation of the grading of preneoplastic and neoplastic lesions of the prostate and breast. In these lesions the application of a BBN allowed the achievement of a level of reproducibility greater than when the grading system was applied on a purely morphological evaluation. The BBN developed by Dr Hamilton was based on the Fuhrman system. Four different grades were in fact included in the decision node and the features and their outcomes for the descendant nodes were also derived from the detailed description given by Dr Fuhrman *etal.* Initial data showed that this diagnostic decision support system allows an accurate analysis of the lesion grade, this being expressed by the corresponding probabilistic measure of belief. The application of such a system shows a certain number of advantages, usually not seen with the morphological approach to grading. The most important is the possibility of expanding the BBN whenever new features are available for evaluation and, at the

same time, of discarding those that show a poor contribution to the grading results. Different types of features can be included. These can be of pure histomorphological type or they can be related to proliferation or morphometrical analysis.

Conclusions

Epithelial tumors of the adult kidney, in particular ROC, represent a variety of neoplasms that can be classified according to morphology and genotype. There is evidence to indicate that tumor stage is one of the most important prognostic factors, irrespective of tumor subtype. The problem of a more objective nuclear grading is still open. The use of diagnostic decision support systems offers the possibility of a flexible approach to this problem while still using morphological criteria.

Papillary (chromophil) renal cell carcinoma

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Papillary reff~l cell carcinoma (ROC), a well-established subtype of RCC, is the second most common carcinoma arising from the renal tubular epithelium and comprises 10-15% of cases in surgical series (1). To be considered a papillary renal cell carcinoma, at least 75% of the tumor is required to be composed of a papillary or tubulopapillary histology with fibrovascular cores (2). These tumors also have characteristic immunohistochemical and genetic features that separate them from other RCCs. However, the term papillary does not encompass all the morphological variations of this neoplasm. Many tumors have wide areas of tubular architecture, or they may be composed of solid sheets of cells without true papillae, but otherwise resemble papillary RCC. This last category has been called the solid variant of papillary HOC (3). For these reasons, the name chromophil RCC was proposed in the Mainz classification (4) to describe the neoplasm. This name signifies that the definition is not based solely on the papillary architecture.

Papillary RCC shows predominance in males of approximately 2:1. The age range is wide, from early adulthood to old age, the average being between 55 and 60 years.

Grossly, it is a well-circumscribed, globular, brown or tan tumor. Hemorrhage and necrosis are frequent. The cut surface is frequently granular and friable. The tumor may appear cystic. Commonly, there is a thick rim of dense fibrous tissue that forms a pseudocapsule in the larger tumors. Calcifications may be present. In surgical pathology, the mean tumor size is 7 cm (2, 5). Bilaterality it is observed in 4.8% and multifocality in 38.7% of the patients (2). Compared with nonpapillary RCCs, papillary RCCs are more common in end-stage kidney disease, are more frequently multifocal and are more often associated with adenomas.

Microscopically, the diagnosis of the neoplasm is based on architectural and cytoplasmic features. More than 90% of papillary RCCs have predominantly papillary or tubulopapillary architecture. The papillae consist of delicate fibrovascular cores covered by a single layer of carcinoma cells. The pattern of papillae is variable, ranging from complicated branching to parallel arrays of long papillae. This last appearance has been termed the trabecular pattern (6). The papillae may contain foamy macrophages and/or psammoma bodies or may be wide and sclerotic (6). The tubular architecture consists of small tubules lined by a single layer of cells similar to those covering the papillae. Rarely, papillary RCC is composed of solid sheets of cells with distinct micronodules that resemble abortive papillae or form ill-defined tubules. These are solid variants of papillary RCC (3). The cells of papillary RCC are classified into type 1 and type 2 (5). Type 1 cells are small, with pale cytoplasm and small oval nuclei with inconspicuous nucleoli. Type 2 cells are large, with abundant eosinophilic cytoplasm and large spherical nuclei with prominent nucleoli. These cells show pseudostratification. Tumors made up of type 2 cells are larger, more common in patients younger than 40 years and are more frequently stage 3 or 4 than tumors made up of type 1 cells (5). Papillary RCC is generally considered a non-mucin-producing tumor. However, this statement is not absolute. The neoplasm may present acid-mucin secretion. We have demonstrated that this mucin secretion can be either cytoplasmic or luminal (7). This observation has a practical value in the differential diagnosis of intrarenal or extrarenal tumors. Trisomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20 and loss of the Y-chromosome are the most consistent genetic alterations (8) in papillary RCC.

The main differential diagnosis of papillary RCC includes papillary renal cell adenoma, metanephric adenoma and collecting duct carcinoma. The diagnostic criteria for papillary adenoma of the kidney comprise: i) papillary, tubular, or tubulopapillary architecture; ii) a diameter less than or equal to 5 mm; iii) histological nonresemblance to clear cell, chromophobe or collecting duct RCC; and iv) cytogenetic abnormalities limited to ±7,+17, and —Y (9). Metanephric adenoma is a rare neoplasm composed of tubular or tubulopapillary structures and glomeruloid bodies of small cuboidal cells. Cytogenetically, the tumor may show normal karyotype or gain of chromosomes 7 and 17 and loss of the Y-chromosome. This supports the hypothesis that the tumor is related to papillary renal adenoma and to RCC. Collecting duct carcinoma diffusely infiltrates the kidney, elicits a desmoplastic stromal reaction and acute inflammation presents frequent figures of vascular invasion and shows reactivity for CK19, 3413E12 and UEA-1 (10).

References

1. Sthrkel 5, Eble JN, Adlakha K at al. *Classification of renal cell carcinoma.* Workgroup No 1. Cancer 1997; aC: 987-989.
2. Amin MB, corlass CL, Renshaw AA eta!. *Papillary (chromophil) renal cell carcinoma: Histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 62 cases.* Am J Surg Pathol 1997; 21: 621-635.
3. *Renshaw* AA, Zhang H, Corlass CL at al. *Solid variants of papillary (chro. mophil) renal cell carcinoma: Clinicopathologic and genetic features.* Am J Surg Pathol 1997; 21:1203-1209.
4. Thoanee W, Storkal 5, Rumpelt HJ. *Histopathology and classification ofrenal cell tumors (adenomas, oncocytomas and carcinomas) the basic cytological and histopathological elements and their use for diagnostics.* Pathol Has Pract 1986; 161: 125-143.
5. Dalahunt B, Ebla JN. *Papillary renal cell carcinoma: A clinicopathologic and immunohistochemical study of 105 tumors.* Mod Pathol 1997; 10: 537544.
6. Ranshaw AA, Corless CL. *Papillary renal cell carcinoma. Histology and immunohistochemistry Am* J Surg Pathol 1995; 19: 842-649.
7. Val-Bernal JE, Obmaz-Romfin JJ, Vailma T at al. *Papillary (chromophil) renal cell carcinoma with mucinous secretion.* Pathol Rae Pract 1999; 195: 11-17.
8. Kovacs O, Akhtar M, Beckwith BJ at al. *The Heidelberg classification of renal cell tumors.* J Pathol 1997; 183: 131-133.