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Pathology of Renal Tumors in Adults. Molecular Biology, Histopathological Diagnosis and Prognosis

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Malignant renal tumors constitute 3% of human cancers, although their frequency differs greatly in various areas. Since the fifties, the incidence of renal cancers has been increasing, but at the some time the prognosis has been improving. In particular, in the last years, several new treatment modalities have been introduced, relying on the understanding of renal cancer biology. The identified etiological factors include smoking, increased body mass, dietary factors and chronic renal disease.

There are several renal tumor types differing in morphology, molecular genetics and biology. Inactivation of the VHL gene leads to formation of the most frequent form in adults, namely clear cell carcinoma. The VHL gene product, a component of an ubiquitin-ligase complex, regulates expression of several genes. Papillary carcinomas depend mainly on the HGF receptor gene (c-Met) activating mutations. At least two types of papillary carcinomas exist, which have different morphology and prognosis. The molecular biology of chromophobe carcinoma and oncocytoma is poorly understood. Differential diagnosis of these tumors is particularly difficult and may require extensive immunohistochemical and molecular studies. Collecting duct carcinoma and medullary carcinoma are extremely aggressive but rare tumors. Some renal tumors have been described or recognized only relatively recently; these newer entities include multilocular cystic clear cell carcinoma, spindle cell papillary mucinous carcinoma, tubulocystic carcinoma, renal epithelial and stromal tumor, epithelioid and oncocytic angiomyolipoma. Besides histological typing, the prognostic factors include tumor stage, grade and several immunohistochemical and molecular markers that are currently under elaboration.

The improved prognosis in renal cancer depends on earlier detection, but also on refinement of therapeutic methods. Small tumors may currently be treated by partial nephrectomy or radiofrequency ablation and larger ones by a laparoscopic approach. All these methods seem to give satisfactory results with low morbidity and mortality rates. Renal carcinoma is notorious for its low sensitivity to chemotherapy and radiotherapy. For several years, immunological treatment with IL-2 and INF-α was the only adjuvant therapy method. However, recently several new drugs have been introduced; they act on tyrosine-kinase receptors, VEGF, c-Met or mTOR pathway. With this progress, perfect understanding of renal tumor biology and exact histological diagnosis have become of prime practical importance.

Epidemiology

Renal tumors account for 3% of all cancers in males and for a lower proportion in females [15]. The worldwide incidence is 4.7/100,000/year in males and 2.5 in females, resulting in around 210,000 new cases annually. Mortality is 2.3 and 1.2/100000/year, in males and females, respectively, resulting in 100,000 cancer-related deaths [418]. A high incidence is observed in North America, Australia and some European countries. A low incidence is noted in Africa, most of Asia and Pacific [105, 418]. The incidence in Europe is also varied between different countries. The highest incidence is seen in the Czech Republic, following a high cancer incidence in general; the lowest is seen in the Former Yugoslav Republic of Macedonia. Poland is a moderate-incidence area [599, 600, 601, 602, 603, 604, 605, 606, 607].

An increase in renal tumor incidence is repetitiously reported. For the USA, the said increase observed since

the fifties is estimated as 125% [460]. Between 1975 and 1995, the annual rise in incidence was estimated by Chow to amount to 2.3-4.3%. The lowest increase rate was noted in white males and the highest in black females [85]. A rise in incidence was reported in different areas, such as North Korea [81, 255], Japan [355], United Kingdom [536] or Spain [21]. On the other hand, the most recent data show a decline in the rising tendency, or even a drop in the incidence rate, at least in Europe. According to Levi et al, this is especially true for Scandinavian countries [313]. In the paper by Levi et al, there is a large gap in Polish data; however, the Polish National Cancer Database and Oncology Institute figures show an analogous trend: renal cancer incidence and mortality increased gradually since the sixties until mid-nineties, and then a plateau and reduction might be observed (Fig. 1) [599, 600, 601, 602, 603, 604, 605, 606, 607].

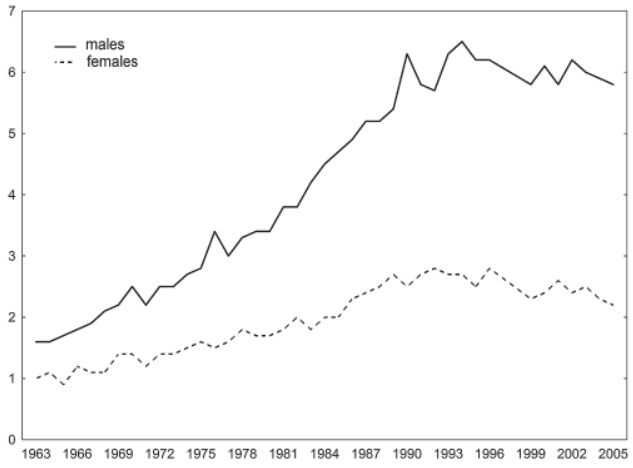

Fig. 1. Renal cancer mortality in Poland according to the data of the Oncology Center cancer register [599-607].

Some information on epidemiology may be derived from autopsy studies as well. Wunderlich et al. reported a 15 to 20% increase of renal cell carcinoma between 1985 and 1995 [583, 584]; this increase is obviously not affected by better diagnostic modalities, which is the case in surgical series. Autopsy results suggest the RCC increase to be independent of an increased detection rate. Similar suggestions may be drawn from the work of Chow et al. describing a relatively constant rate of renal pelvis carcinomas in comparison to tumors of the renal parenchyma [85].

The autopsy series differ from the usual, surgical material. The former contains a greater number of smaller and benign tumors. There are also lesions seen predominantly in postmortem examinations. For example, Reis et al. found 89 fibromas and 20 adenomas among 500 autopsies [449]. Alanen et al. noted 112 renal tumors in 8489 autopsies [13], and Kihira et al. reported 51 renal cell carcinomas (RCCs) in 7970 autopsies (0.65%). Half of these were not recognized clinically [253]. In our material [282], 97 renal tumor autopsies were seen in 3512 postmortem exams. Half of the detected tumors were benign; among the malignant tumors, the papillary type was much more prevalent that in surgical material. Although the increased incidence was followed by an increased mortality, 5-year survival rates improved significantly [243, 414, 460]. This is explained by a general increase in longevity, improved imaging modalities, earlier diagnosis and stage migration, better staging methods, improvements in surgical technique and introduction of adjuvant treatment methods, such as immunotherapy [190]. On a national scale, renal cancer constitutes an important economical burden. In the USA, over 51,000 new cases are diagnosed annually, what results in $ 4,400,000,000 overall societal cost. A large majority of these costs are direct treatment expenses [16, 297, 388].

Symptoms and Diagnosis

One of the most frequent clinical symptoms is gross hematuria [166]. The classic triad of hematuria, pain and palpable mass is not as classic anymore, as it is currently seen in a considerable minority (5%) of cases [166]. This is mainly due to stage migration. In fact, the currently diagnosed RCCs are smaller than in the past and a tendency for renal tumors to decrease in size still persists [99]. Other symptoms are unexpected fever, loss of body weight, loss of appetite or paraneoplastic syndromes. The most frequent are hypercalcemia, polycythemia or anemia, hypertension, amyloidosis or gynecomastia. In some cases the tumor presents with metastatic disease, sometimes a single metastatic focus that requires distinction from an extrarenal primary lesion [140].

No specific laboratory method is used, although an extensive search for such methods is in progress. For example, a rise in serum VEGF and HGF level was reported. The level of these growth factors correlates with tumor stage [231, 535].

Biopsy

Renal tumors are usually diagnosed before operation by imaging methods only. The main reason is that a vast majority of radiologically detected tumors is malignant. Additionally, in several cases, additional tumors are present, which may be malignant as well. In autopsy series, multiple

TABLE 1
Renal tumor classification – a historical prospective

1979 [467, 468]	1994 [383]	1998 [6]	2004 [140]	Comment
Renal cell carcinoma (hypernephroma)	Clear cell (hypernephroid) carcinoma	Clear cell carcinoma	Clear cell renal cell carcinoma	
		Cyst-associated renal cell carcinoma Renal cell carcinoma originating in a cyst Cystic renal cell carcinoma	Multilocular clear cell renal cell carcinoma	
	Papillary carcinoma	Papillary renal cell carcinoma	Papillary renal cell carcinoma	
	Granular cell carcinoma	Granular cell carcinoma	-	currently included with clear cell or chromophobe carcinomas
	Chromophobe cell carcinoma	Chromophobe cell carcinoma	Chromophobe renal cell carcinoma	
	Sarcomatoid carcinoma	Spindle cell carcinoma	-	currently classified according to the non-sarcomatoid component
	Collecting duct carcinoma	Collecting-duct carcinoma	Collecting-duct carcinoma Renal medullary carcinoma	
			Xp11 translocation carcinomas Carcinoma associated with neuroblastoma Mucinous tubular and spindle cell carcinoma	} most recently described entities
			Renal cell carcinoma, unclassified	
Cortical adenoma	Renal cortical adenoma	Papillary/tubulopapillary adenoma	Papillary adenoma	
	Oncocytoma	Oncocytic adenoma (oncocytoma)	Oncocytoma	

tumors may constitute as much as 14% of cases [583]. In multiple renal tumors, only in 19% all the foci are benign and in 48% all the foci are malignant. In as much as 33% of multifocal tumors, both malignant and benign tumors are present in the same kidney. In the series described by Gudbjartsson et al, two of 45 oncocytomas were accompanied by smaller renal cell carcinomas [191]. Consequently, a biopsy of the largest tumor may not be representative of the most important lesion. Tumor seeding along the needle tract is also a potential risk, prompting the clinicians to be reluctant to use renal tumor biopsy [69, 178, 262].

In the recent years, some renaissance of interest in renal biopsy may be noted [295]. This renaissance is due to stage migration, with a higher percentage of small lesions being detected by imaging studies. Indeed, the mean size of renal tumors decreased significantly in the last 10 years [99]. In addition, treatment methods alternative to radical nephrectomy are currently available. Some of these methods, like radiofrequency ablation, will hamper histological postoperative diagnosis. According to Renshaw et al, thin needle aspiration biopsy may properly classify 3/4 of renal tumors [451, 454]. Reichelt et al. analyzed the performance of core needle biopsy and obtained appropriate categorization in 85% [448]. In the series analyzed by Kummerlin et al, the sensitivity was 80% and specificity reached 100% [287]. In the meta-analysis of Lane et al, the rate of clinically important complications was acceptable (5%) and kidney loss or death seemed to be very rare. The material was insufficient for diagnosis in 5% and the diagnosis was indeterminate in additional 4% of cases [295]. Obviously, some histological types may be more difficult to distinguish; in particular, the type difficult to recognize is chromophobe carcinoma; this is also true for surgical material.

The frequency of histological types in tumors of various sizes may differ: in the series of McKiernan et al, which consisted of partial nephrectomy specimens (an average tumor diameter of 2.7 cm), clear cell carcinoma accounted for only 51%, papillary carcinoma for 18%, oncocytoma for 11%and chromophobe carcinoma for 7% [364]. The data from our Department is shown in the Table 2. Of note is over-representation of papillary tumors among the smallest lesions. These differences fall short of the threshold of statistical significance, however. A similar trend is seen also in our autopsy series [282].

Etiology and Risk Factors

The best documented risk factors of renal cell carcinoma are tobacco smoking, obesity, arterial hypertension and medications used in hypertension, diuretics and chemical carcinogens, such as arsenic compounds, asbestos, organic solvents and thorotrast. Genetic factors are obviously also involved, with the incidence higher in Africans; however, strictly speaking, familial cases are relatively rare (4%). Renal cancer is also significantly more prevalent among patients with chronic renal disease and scarring, after renal transplantation and in congenital renal defects, such as horseshoe kidney [47, 127, 227, 365, 382, 418, 492, 562]. The role of obesity has been extensively investigated. This factor is said to be particularly important in females, in whom body mass index (BMI) over 30 increases the renal cell carcinoma risk 1.52-fold [447]. Bergstrom believes, however, that the BMI-renal cancer relationship is not sex-dependent; according to the investigator, a one-unit increase of BMI yields a 1.07-fold increase of risk [47]. In the opinion of the same author, 25% of European renal cancers are potentially avoidable by change of lifestyle [49]. In males, smoking may be an even more important etiologic factor [44, 562]. Tobacco smoking was indeed the first risk factor identified [46]. Polish epidemiological studies report the correlation coefficient between renal cancer mortality and tobacco consumption r=0.45 for females and 0.62 for males. The increase of renal cancer incidence parallels the increase of smoking frequency. The mortality rate for renal cancer is correlated with mortality for pancreatic (r=0.43) and pulmonary (r=0.53) cancer [607]. Obviously, both tumors are strongly tobacco-dependent. Smoking may also be partially responsible for sex-related difference in incidence [243]. Quitting smoking causes a fall in renal cancer incidence; however, the rate of such a fall is slow, with a significant

TABLE 2
Relationship between tumor diameter and histological diagnosis

Diameter [cm]	Clear cell carcinoma	Papillary carcinoma	Chromophobe carcinoma	Oncocytoma
<4	79.43%	12.06%	3.55%	4.96%
4-7	83.44%	8.13%	5.94%	2.50%
>7	83.25%	6.28%	7.33%	3.14%

to reduction after 20 years and a fall to population risk only after 30 years after smoking cessation [415]. This explains why the reduction of renal cancer incidence has been observed only recently and is not as evident as the reduction of pulmonary cancer incidence. Other environmental pollutants may be also involved: renal cancer incidence is also higher in urban areas [244]. In Poland, the urban/rural index is 1.5 for females and 1.8 for males [607].

Endocrine factors might be in part responsible for the sex related difference in incidence. The results of research are somewhat contradictory, but Mulukwu et al. have shown that lifetime length of ovulation time is inversely correlated with the renal cancer risk. The exogenous estrogens enhance the risk as well [373]. On the other hand, according to data published by Karolinska Institutet, each pregnancy increases the risk by 15% [293]. Animal studies suggest that in renal tubular epithelial cells exposed to estrogens, free radical are formed, damaging DNA and lipids with an obvious carcinogenic effect [169, 170]. The estrogen receptor (ER) gene polymorphism may also modulate the renal cancer risk. Indeed, differences in frequency of the ER gene variants in renal cancer patients and general population were shown [534]. Estrogens may be also involved in renal cell carcinoma-overweight relationship, as the latter causes increased estrogen levels. The renal carcinoma itself expresses ER in about 1% of cases only, but in 15% of cases the androgen receptor (AR) may be detected. AR is seen mainly in low stage, low grade tumors and rather in male subjects [300]. Tamoxifen may have some beneficial effect on advanced RCC, but this might be also due to protein kinase C inhibition [586]. Intrauterine factors may affect the future susceptibility to RCC: a high birth weight may increase the risk, especially in males without hypertension or diabetes. These suggestions are in contrast with recent reports of low birth weight as a risk factor of chronic renal damage [48].

In chronic renal disease, acquired polycystic kidney and after renal transplantation, RCC frequency is significantly increased. In autopsy series of chronic renal failure patients, renal cancer frequency has been reported to reach 45% [63, 567] Ishikawa estimates RCC incidence in renal transplant patients to be 1 for 178 cases per year [228]. This effect may be due to renal scarring, free radicals generation in a chronically ill kidney, but also to immunosuppression. The immunosuppression modality may affect the risk, with an increase caused by alkylating agents and a decrease by rapamycin derivates [566].

Moderate physical activity is supposed to be protective; this effect is in part independent of body weight [382, 562]. Other protective factors may be a vegetable-rich diet, especially containing citrus fruits [207, 365] and also low alcohol intake [492].

Classification

Older classification systems recognized an increasing number of more or less defined entities. The relationship between these entities was obscure and their clinical significance uncertain [6, 383, 517, 539]. In the last 20 years, an increasing body of knowledge of renal tumors biology and their genetic background have allowed for establishment of categories that constitute true entities. This was finalized in the new WHO classification; the classification is not complete, however, as new entities are being described and details of the old ones refined [140, 431, 450]. A very interesting feature of renal tumors in this classification is a strong relationship between morphology and genetics, in contrast to tumors in other common locations. Gene microarray experiments lead to formation of clusters that are quite compatible with morphological categories [179, 527].

The mostimportant renal tumor categories are clear cell (conventional) carcinoma, papillary carcinoma, chromophobe carcinoma and oncocytoma [158, 450, 458, 459]. Several minor entities do exist and new ones are added and will likely be added in the future [527]. With the introduction of new more specific treatment modalities, it is important to focus on the precise histopathologic diagnosis [278, 325].

Clear cell (conventional) carcinoma

This is the most frequent form of renal tumor in adults. Clear cell carcinoma (CCRCC) is composed of cells with clear, „empty" cytoplasm, containing abundant glycogen. Cell borders are prominent and the nuclei may show a different degree of pleomorphism, raging from small, round and regular to large, hyperchromatic and bizarre. Grossly, the lesion is usually well-circumscribed, with a characteristic yellowish to light-orange color, often containing irregular whitish, hyaline, or reddish, hemorrhagic areas. CCRCC, especially low-grade variants, superficially resembles the adrenal cortex, a fact that has led Virchows and Gravitz to propose the pathogenic link with adrenal rests. Modern notions about histogenesis were founded in the sixties. Electron microscopy allowed for identification of brush border on the apical and cellular membrane invaginations on the basal side; these features defined CCRCC as a proximal-tubule derived tumor [394, 539]. In some cases, the cytoplasm is eosinophilic and granular. In electron microscopy, increased mitochondria are seen in these cases. The mitochondria are irregular and show structural defects. Such cases were previously regarded as a separate tumor category and termed "granular"; however it has been demonstrated that they share the same molecular mechanism as the bulk of CCRCCs. Their biology is also identical, stage

by stage and grade by grade, to that of more usual carcinomas [140, 163, 539, 547].

The most important familial syndrome related to CCRCC is von Hippel-Lindau disease (MIM 193300 [234]). It is important not merely due to its frequency, but rather as a source of knowledge about RCC pathogenesis [140, 259]. In von Hippel-Lindau syndrome, several highly vascularized tumors may be observed, such as cerebellar and ocular hemangioblastoma, and CCRCC itself. Some types of the syndrome may be distinguished: type I has no pheochromocytoma that is typical for type II. In type IIA, the RCC risk is low, but in type IIB, the RCC risk is high. In a rare type IIC, pheochromocytoma is the only manifestation. The difference in phenotype depends on the specific type and location of the mutation of the same VHL gene, leading to different degrees of loss-of-function of the VHL protein [234, 259]. The renal lesions are often multiple and include cysts, cystic tumors and solid CCRCCs. The progression from a cyst, through a cyst with epithelial hyperplasia, cystic tumor to solid, typical CCRCC was described [436].

The genetic background of sporadic CCRCC is also linked to 3p alterations, in particular the VHL gene changes, including mutations and promoter methylation [171, 181, 209, 225, 259, 337]. Another hypothetical tumor suppressor gene involved was mapped on 3p12 (NRC-1, MIM 604442 [234]), but has not been further characterized [334]. In the vicinity lies the fragile histidine triad locus (FHIT) (3p14.2, MIM 601153 [234]). FHIT participates in t(3; 8) translocation, seen in some familial RCC cases. However, the pathogenesis of this familial form may be related to the second participant of the translocation, TRC8 (locus 8q24.1, MIM 603046 [234]). The TRC8 gene product is, like pVHL, a component of E3 ubiquitin ligase. It is of interest that the other components of pVHL-related E3 ligase (elongin B, elongin C, cul2, Rbx1) appear not to be altered in CCRCC [92]. Another gene mutated in some CCRCCs is OGG1 (locus 3p26.2, MIM 601982 [234]) responsible for repair of free radicals-related DNA defects [31]. In 3p there is also located the gene for plexin B1 (601053 [234]); its protein product is present in normal tubular epithelial cells, but is absent in 80% of CCRCC [184]. Plexin B1 may participate in cell adhesion, motility regulation and apoptosis. Alterations of 5q22, deletions of 8p, 14q, 6q, 9p21-22 and chromosome 9 monosomy were also described in CCRCC [512]. Of these, deletions of 8p, 9p and 14q were linked to tumor progression [66], as was c-Met expression [83]. Another signaling pathway, recently reported to be constitutively activated in CCRCC, is Notch [503]. This would be responsible for VHL-independent growth stimulation, and its blocking by siRNA inhibits tumor growth. Consequently, this pathway would be a possible therapeutic target.

Not all the functions of pVHL are known; the best understood and evidenced is its participation in an ubiquitin E3 ligase. This ligase marks the hypoxia inducible factor α (HIF) for proteolytic removal (Fig. 2). The functions of two homologues HIF1-α and HIF2-α are usually regarded as complementary, but in the RCC cell culture, HIF2-α may be more pro-proliferative [445]. HIF2-α may affect the VEGF production in a pVHL independent manner [498]. Both HIF1-α and HIF2-α are constantly produced, but if oxygen level is normal, they are rapidly removed. In hypoxia, HIF1-α and HIF2-α accumulate and connect to HIFβ, forming a transcription factor. pVHL is inversely correlated with nuclear HIF1-α expression that is an indicator of a poorer prognosis [128, 269]. HIF controls the expression of several genes involved in adaptation to low oxygen levels. These genes include PDGF, bFGF, TGF-α, EGFR, erythropoietin, carbonic anhydrase IX, GLUT-1, iNOS, VEGF-A, mTOR elements and CXCR3 [115, 193, 240, 241, 259, 269, 274, 360, 461]. In CCRCC, these factors are thought to be directly responsible for autocrine cell growth stimulation and extensive neoangiogenesis [45, 102, 151, 152, 160, 269, 325, 489, 578].

When transfected into an RCC cell line, wild-type VHL will decrease tumor formation in vivo, but does not prevent tumor growth in vitro [226]. Interestingly, VHL-deficient rodents have the phenotype unlike the human VHL disease. The genotype VHL-/VHL- is lethal, and VHL+/VHL- mice do not exhibit an increased susceptibility to renal tumors, either spontaneous or induced by chemical carcinogen (streptozocin) administration [182]. Vascular lesions are, however, seen in 20% of the transfected mice. These lesions, located in the liver, spleen, uterus, ovaries or heart may have different morphology, ranging from vascular dilatations to angiosarcomas. Streptozocin does exert an enhancing effect on tumor formation [271] In rats, HIF2-α stabilization may be caused by TSC2 gene inactivation [326]; it is not clear whether such a side-mechanism might be functioning in human sporadic RCC.

It was hypothesized that HIF1-α might induce genetic damage and instability by increasing free radicals generation [210]; however, this was denied by other studies [306]. Microsatellite instability was reported as rare in RCC, but this claim was based on small series [104, 301]. Chen et al. described mutations in hMSH2 and β–DNA polymerase in a RCC cell line [80]. Deguchi et al. described decreased hMLH1 and mMSH3 mRNA in RCC [118]. Baiyee and Banner analyzed MLH1 and MSH2 expression in different types of RCC. They showed loss of these proteins, particularly in CCRCC (20-40% of cases). Interestingly, in papillary carcinoma, MLH1 was affected, and in chromophobe carcinoma, only MSH2 was affected. These studies were done in a small number of cases however [37]. The relation-

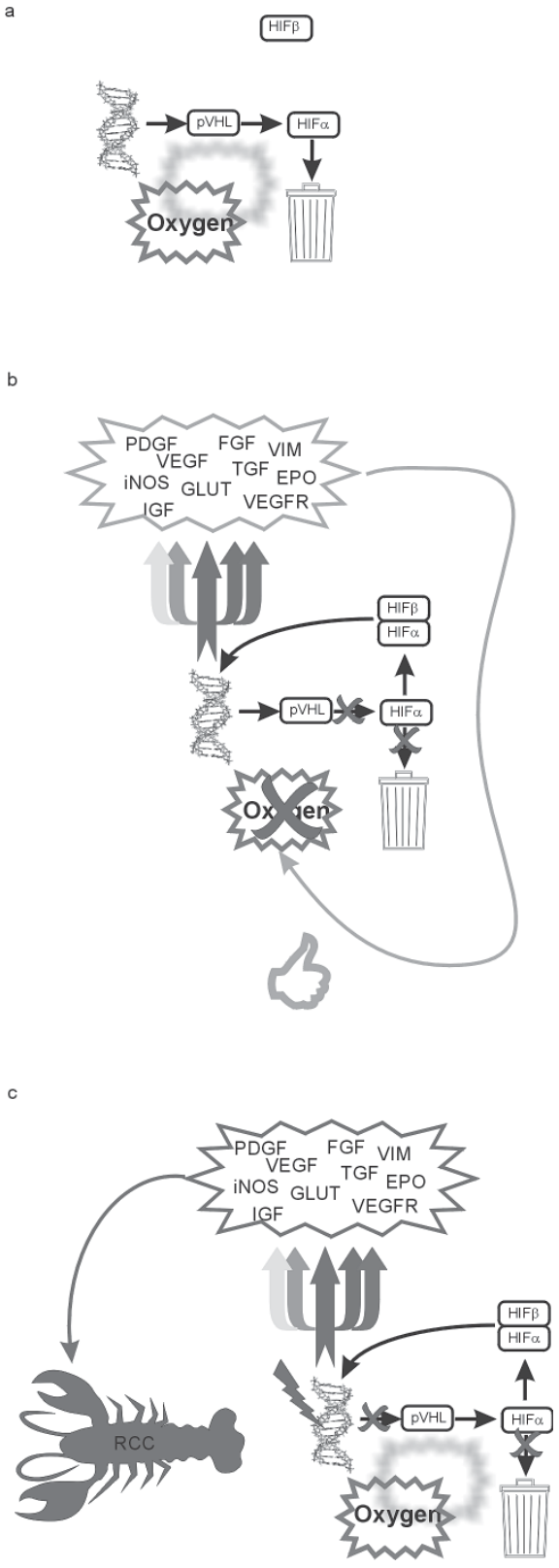

Fig. 2. The role of pVHL and dependent signaling pathway in the pathogenesis of clear cell carcinoma: a) normal conditions, b) hypoxia and the role of VHL/HIF in adaptation to hypoxia, c) loss-of-function of pVHL leads to overexpression of growth factors and cancer development.

ship of chromophobe carcinoma with genetic instability in general is also of interest, because of its tendency towards progression to sarcomatoid type [9]. Another DNA-repair gene altered in RCC is OGG1. Its protein product participates in repair of DNA defects dependent on guanine oxidation by free radicals [31].

One of the most important growth factors in CCRCC pathogenesis is VEGF-A. Yilmazer et al. demonstrated a correlation between VEGF-A expression, microvascular density, stage and grade of the tumor. Interestingly, in their material the highest VEGF-A expression was seen in papillary and not in clear cell RCC [595]. The VEGF content in the tumor is significantly higher than in normal renal tissue. This increase depends mainly on $VEGF_{121}$, the most soluble isoform [464]. In cases with high VEGF-A expression, survival is significantly shorter. Also, VEGFR-1 expression is enhanced, but VEGFR-2 seems not to be increased. Rivet et al. showed that tumor cells coexpress VEGF-A and VEGFR-1. No such phenomenon is encountered in a non-neoplastic kidney [464]. VEGF-A may be derived not only from tumor cells, but also from the stromal ones. Nauman et al, showed an increased cyclin E expression both in the tumor and in its neighborhood [390]. VEGF-A is increased also in RCC patients` blood; its serum level is correlated with tissue level expression, tumor grade stage and tumor necrosis [462]. VEGF-A was also shown to be increasingly secreted in the urine [77]; the urine VEGF-A level is higher in less differentiated tumors, but is not correlated with microvascular density, tumor size or histologic type. According to Chang et al, other, poorly characterized factors may affect angiogenesis to a greater degree than VEGF-A does [77]. Kurban et al. showed that VHL suppression affected angiogenesis by enhancing metalloproteinase expression [288]. Another factor affecting vessel formation is found in mast cells; mast cell density is correlated with microvascular density, but not with tumor stage or grade [557].

In addition to features of small vessels inside the tumor itself, it may be interesting to examine changes in larger vessels outside the tumor mass. Tomic et al. initiated such research, concentrating on the renal artery. They showed significant differences in arterial wall thickness between the RCC and control groups. The most prominent observation was the thickening of the internal lamina. Also the frequency of fibromuscular dysplasia is increased among RCC patients [550, 551]. In this vascular remodeling, mediators produced by the tumor might be involved, but the subject requires further research.

CCRCC metastasizes mainly by the hematogenous route. The most frequent locations of the metastases are the lung, bone, brain, liver and adrenal gland. Some of the multiple tumors are in fact intrarenal metastases [166, 456].

The principal pathways responsible for bone resorption and metastatic growth depend on EGF and TGF-β. In animal models, receptor blocking results in slowing the metastatic growth; this has a potential for a clinical application [580], however, the effectiveness of such a treatment has been questioned [247, 304]. Daniel et al. showed that 15% of CCRCCs express NCAM. NCAM expression is correlated not only with stage and grade, but specifically with the risk of adrenal and central nervous system metastases [110].

On histochemistry, CCRCC has characteristic cytokeratin and vimentin co-expression [505]. In non-neoplastic tubular epithelial cells, the appearance of vimentin is indicative of damage and dedifferentiation [189]. The evidence of proximal tubular differentiation is found in expression of MUC3, aquaporin-1, N-cadherin and cadherin-6 [53, 311, 362]. CD10 (CALLA) antigen is a metaloendopeptidase present on the surface of several cell types, but it is particularly strongly expressed on renal tubular proximal cell brush border. As it is retained in most tumors, it is a useful marker for tumors derived from proximal tubules; however, it may be expressed in tumors of many other primary locations. Yang et al. proposed to use CD10 for differential diagnosis between renal and adrenal tumors; RCC was positive in 90%, but tumors of adrenals in 20% only [590]; anyway, it is obvious that these results indicate a need for caution. An alternative marker is antibody against RCC antigen (GP200). In a normal kidney, GP200 is expressed on proximal tubular brush border, like CD10; it is present on 70% of RCCs, most often of the proximal tubular lineage. The chromophobe carcinomas are, however, positive in 15% [493]. The expression is seen mainly in tumors of the proximal derivation. This marker was regarded as very specific and quite sensitive; however, it was realized that GP200 may be expressed in as many as 1/3 of other cancers, most often breast carcinoma, colorectal carcinoma, ovarian carcinoma, adrenal carcinoma and melanoma [38, 506]. On the other hand, in sarcomatoid carcinoma, only 20% of tumors may be positive, and in metastases, where it would be most useful, it is expressed in 40% only [493]. Cytokeratins present on CCRCC are mainly CK8 and CK18 [505, 506], whereas CK7 is expressed rarely [357, 362]. Tamaskar et al. reported membranous expression of caveolin-1 as quite specific for CCRCC. The stain was positive in 86% of CCRCC cases, but was present in only 5% of papillary carcinomas or oncocytomas. Chromophobe carcinomas were entirely negative. The cytoplasmic reactivity was similar in all histological types [532]. PAX-2 is a transcription factor interacting with WT-1 pathway, important for urinary tract development. It is expressed in a developing kidney and in kidney tumors, including nephroblastoma [510]. In a normal adult kidney, PAX-2 would be expressed in some collective duct cells [111]. It was shown that blocking PAX-2 expression decreases proliferation of RCC cells [180]. It is expressed mainly in CCRCC; the presence of PAX-2 in papillary carcinoma seems inconstant; none or almost no reactivity is present in chromophobe carcinoma, oncocytoma, collecting duct carcinoma and urothelial carcinoma. A correlation of PAX-2 with proliferation index and tumor grade was observed. PAX-2 expression is also stronger in tumors with metastatic spread [111, 362]. Another potential marker of CCRCC is glutathione S-transferase α 2 and 3. Its function is unknown, but this enzyme may participate in the resistance to chemotherapy [527].

Multilocular cystic clear cell carcinoma

Several renal clear cell carcinomas are in a larger or smaller part cystic. Some of these should be distinguished because of their somewhat different morphology and biology. These are tumors consisting of a multilocular cyst, lined with one or focally more layers of cells with clear cytoplasm. The nuclei are rather small, round, with inconspicuous nucleoli. If the Fuhrman system is applied, they represent grade 1 or more rarely grade 2. Some of the cysts may loose their epithelial lining. No larger tumor cell collections are usually seen. In particular, grossly evident collections of cells and significant necrosis place the lesion in the conventional clear cell category. The practical importance of multilocular cystic clear cell carcinoma lies in its very low grade and a very good prognosis. In fact, no metastatic behavior was described. The molecular mechanism underlying the tumor is the very same mechanism of classic clear cell carcinoma. The diagnosis of multilocular cystic clear cell carcinoma often requires the use of immunohistochemistry in order to prove the epithelial nature of cystic lining. However, as none of such cystic, poorly-cellular lesions is aggressive, this differential diagnosis is of limited practical significance. Much more important is to exclude tumors with larger neoplastic foci, or lesions with cysts resulting from extensive necrosis [140, 162, 520].

Papillary carcinoma

This histological type was relatively early identified as a separate entity [350]; in fact, formerly RCC was broadly divided into papillary and non-papillary (i. e. clear cell) types. PapRCC was also called “chromophil”, as - in contrast to CCRCC - the cytoplasm stains with eosin. Papillary carcinoma (PapRCC) would be less extensively vascularized in imaging studies, more frequently necrotic, but less advanced and less aggressive than CCRCC; currently these

characteristics are mainly employed in reference to type 1 PapRCC (vide infra) [18, 19, 161, 366, 372]. The rate of lymph node metastasis is generally higher than in CCRCC. Obviously, metastatic disease cancels all prognostic benefits of the histological type. Indeed, survival was reported to be even shorter than in disseminated CCRCC [456]. PapRCC is frequently multifocal, even in 1/4 of cases. The multifocality does not alter the survival [368]. Genetic studies demonstrate that multiple foci of PapRCC are independent, clonal proliferations; this is in contrast with less frequent "multifocal" CCRCC, which is truly a sign of intrarenal dissemination [235, 238].

Grossly, PapRCC is well circumscribed, usually has a granular, friable surface and tends to be gray. However, some tumors may have yellow color, similar to that of CCRCC, because of a high lipid content in the foamy macrophages. Histologically, PapRCC shows papillae containing fibrovascular cores of varying thickness, covered with one or more layers of epithelial cells. The papillary cores, if prominent, may contain hyalinized fibrous tissue or abundant foamy macrophages. These cells may induce less experienced pathologists to diagnose a clear cell tumor. Traditionally, it is assumed that at least 1/2 of the tumor should be composed of papillae to merit the diagnosis of PapRCC; however, these tumors are usually composed entirely of homonomous structures [140, 431, 450, 514]. In some cases, the small, densely packed papillae are closely apposed, giving an impression of diffuse growth; this variant has been named "solid" [457]. Rare tumors may show the papillary growth pattern and cells with clear cytoplasm. Some of such tumors may be special variants of RCC in neuroblastoma survivors or be related to chromosomal translocation (vide infra); others should be categorized as unclassified RCC. It has been shown, however, that they share the genetic background of CCRCC [167, 478]. Small foci of clear cells are still compatible with the diagnosis of PapRCC. Indeed, this feature was seen in as many as 95% of tumors with typical genetic alterations of PapRCC [336]. A possible confounder here may be autolysis.

The Fuhrman grading system, although widely accepted for CCRCC and used by some for PapRCC as well, seems not to be appropriate. Only the nucleolar size may provide independent prognostic information [499]. Obviously, important prognostic factors are tumor size and stage. In immunohistochemistry, there are positive reactions for cytokeratins 7, 8, 18 and 19, vimentin, RCC antigen, MUC1 and aquaporin-1 [311, 362, 505, 506]. Recently, a constant and strong expression of α methylacyl CoA racemase (AMACR) was described. The function of the enzyme in RCC is unclear [527, 556]. The reaction for CD117 is somewhat controversial; in some reports it was detected in half of cases; however, it was argued that this may be due to cross-reactivity with another, yet non-characterized antigen [316, 411]. On the other hand, c-Kit mutations in intron 17 were described [322]. In most cases, immunohistochemistry is of little use in PapRCC, as it is readily identified in routine staining.

The most constant cytogenetic alterations are trisomies of chromosomes 7 and 17 and deletions on chromosome Y [100, 277, 278]. In some cases there are chromosome 12, 16 and 20 trisomies, and losses of genetic material from chromosome 14 [208, 280, 512]. As in the case of CCRCC, our knowledge about molecular background of PapRCC is largely derived from the analysis of familial cases. Familial PapRCC may be an isolated lesion, inherited as an autosomal dominant trait with incomplete penetrance [609]. The defect lies in the c-Met gene (locus 7q31, MIM 164860 [234]) encoding hepatocyte growth factor (HGF) receptor. The c-Met mutation activates the receptor, leading to constant, ligand-independent, tyrosine-kinase activity that leads to uncontrolled cell proliferation [93, 100, 208, 325, 484, 523]. On histology, in these cases, type 1, well differentiated papillary carcinomas are seen. These are often multiple and they present at an earlier age than sporadic cases [336, 485]. Another cancer syndrome (Reed's) combines renal cell carcinoma with leiomyomatosis; it is also inherited autosomally dominantly with incomplete penetration; the mutation alters the fumarate hydratase gene (FH, locus 1q42.1, MIM 136850, 605839 [234]). The mutation causes loss-of-function of FH, a tricarboxylic acid, or Krebs cycle component [263]. The same gene encodes both FH isoforms, cytoplasmic FH1 and mitochondrial FH2; the molecular background of this differentiation is unclear. Associations between other tricarboxylic acid cycle enzymes and cancer were also described. For example, familial paragangioma depends on succinate dehydrogenase mutation (MIM 168000 [234]). The FH gene inactivation was also detected in sporadic leiomyomas, but not in the examined malignant tumors [307]; indeed, in sporadic renal cancer, FH inactivation is rare [264]. The relationship between FH loss-of-function and cancer remains obscure. It was suggested that loss of FH activity may hamper free radicals removal or stabilize HIF-1α, as succinate dehydrogenase does [475, 487]. FH-deficient families with and without renal tumors share the same mutation locations and types, thus it is supposed that additional modifiers have to be involved [12]. However, it was reported that the differences of age at tumor detection between different families may depend on the exact location of FH mutation [485]. The tumor suppressor action of FH depends, anyway, on its enzymatic activity [12].

Clinically, the main symptoms are multiple leiomyomas, seen in the skin and in the uterus in women. This leiomyomatosis was described as early as in 1958; the coexist-

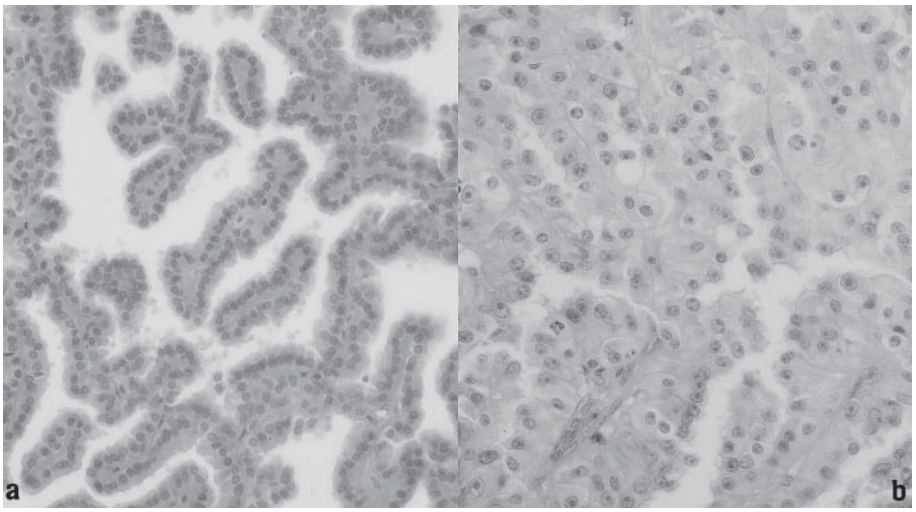

Fig. 3. Papillary carcinoma types: a) type 1. A single layer of cells, the nuclei are round and small, similar in size, b) type 2. Cells with abundant cytoplasm and large, irregular nuclei with prominent nucleoli. Hematoxylin-eosin, magnification 240x.

ence of renal neoplasia was observed much later [174, 263, 272, 552]. Toro et al. described 31 families with FH defect [555]. In five families there were 13 cases of renal cancer. All of them were unilateral and single. On histology, all but one tumor were type 2 papillary carcinomas. The one discordant case was a collecting duct carcinoma. According to Merino et al, the morphologic picture of renal tumors is more variable, and although papillary structures do predominate, tubular or solid growth patterns are common. A characteristic feature might be the nucleus containing a huge, eosinophilic nucleolus surrounded by a clear "halo" [369]. In few cases, clear cell carcinomas may be detected; they share the characteristic nuclei of papillary tumors.

There is some evidence that spontaneous PapRCC follows the pathway of the familial form. On immunohistochemistry, HGF receptor is expressed in almost all cases. In some of these, activating c-Met mutations may be detected. Chromosome 7 trisomy common in PapRCC obviously enhances the activity of c-Met that is located on the chromosome [83, 325, 336, 484]. An alternative stimulatory pathway was proposed by Morris et al. [377]; these authors detected promoter methylation of the HAI2 gene (locus 19q13.1, MIM 605124 [234]) in 40% of PapRCC examined. The HAI2 protein product affects HGF/MET signaling. HAI2 promoter methylation was also present in some CCRCCs. Restoration of the HAI2 function limited the colony stimulating activity, adherence-independent cell growth and motility of tumor cells. Lindor et al. failed to detect germline c-Met mutations in cases of PapRCC without familial history; they concluded that genetic screening is not indicated in such cases [323].

Characteristically, PapRCC is frequent in chronic disease patients. This is especially evident in cases with a prolonged history of renal disease [229]. This is also true for the closely related papillary adenoma (vide infra), which may be present in as many as 18% of chronically ill kidneys [575].

Papillary carcinoma type 1 and type 2

Although many early reports stated that PapRCC is associated with a better prognosis than CCRCC, several other authors expressed contrary views. Delahunt and Eble proposed that all these results may be true indeed, because PapRCC may not be a uniform entity [122]. Two separate types were thus described: type 1 is composed of papillae lined with a single layer of small cells with little cytoplasm and also small, uniform nuclei without visible nucleoli. A relatively dense packing of nuclei with scarce cytoplasm imposes a "blue" look to the lesion observed at low magnification. Type 2 is composed of papillae lined with several layers or pseudolayering cells with abundant, eosinophilic cytoplasm and larger that in type 1, round nuclei with irregular shape and prominent nucleoli (Fig. 3). Type 2 PapRCCs are usually larger and of higher stage than type 1 tumors, their proliferative activity is also higher [123]. A similar classification system was shown by Amin et al; however, here 3 types were described [19]. A higher aggressiveness of type 2 PapRCC was confirmed by some authors. In several reports, the type is the only, apart from tumor stage, independent prognostic factor [123, 194, 368, 372, 432]. The 5-year survival in type 1 may be as high as 90%, whereas in type 2, it is 50% only

[588]. In some reports, PapRCC types are not correlated with tumor stage, but still have a prognostic value [14, 312]. Some authors, however, published different results. Mejean et al. identified prognostic significance of the types only on univariate analysis [368]; other investigators were unable to see any differences in survival between PapRCC types [499, 587].

Cytogenetic analysis shows that both PapRCC types share chromosome 7, 16q and 17q amplifications. Type 1 would present less alterations and type 2 would show additional amplifications and deletions [194, 232]. These results may suggest progression from type 1 to type 2. On the other hand, Sanders et al. detected separate mutation patterns of 17q and 9p, and concluded that PapRCC types develop through separate pathways [481]. 8q amplification might be the factor directly responsible for higher aggressiveness of type 2. Indeed, c-Myc is located on the long arm of chromosome 8 (locus 8q24.12-q24.13, MIM 190080 [234]). This transcription factor induces cellular proliferation and it was shown to be increasingly activated in type 2 PapRCC [165]. If this tumor type indeed develops through type 1 progression, the progression might depend on c-Myc activation.

On immunohistochemistry, strong cytokeratin 7 expression is seen in type 1 only; type 2 expresses rather topoisomerase II α [362, 592]. In type 1, EMA (MUC1) reactivity is seen in all cells and is apical, just in the normal tubular cells. In type 2, single positive cells may be seen only focally [299, 312]. Also reaction for CD10 is more frequent in type 1 [298]. Yang et al. analyzed genetic and clinical features of PapRCC and were able to identify two distinct groups [592]. Comparing these results with morphology, the less aggressive tumor group consisted of lesions identified as type 1 tumors, intermediate tumors and lower grade type 2 tumors; the more aggressive tumor group consisted of high grade type 2 tumors.

Additional PapRCC types might exist, which do not fit into the already classic bimodal scheme. One type, which is getting general acceptance, is oncocytic PapRCC. Its cells have abundant, eosinophilic cytoplasm, in some respect similar to type 2, albeit even more granular, pinkish and indeed "oncocytic". All the same, the nuclei are relatively homogeneous, round, without prominent nucleoli and form a single row, without a tendency towards pseudomultilayering. In electron microscopy, rich mitochondria were detected in the cytoplasm, showing that the term "oncocytic" is not merely a name. Biologically, these tumors would be rather indolent, similarly to type 1 [14, 211, 305]. Mai et al. reported oncocytic PapRCC with an almost completely solid growth pattern and only focal papillae. Such a tumor is very likely to be mistaken for an oncocytoma; however, immunohistochemical features are that of a papillary carcinoma. At the moment, no cytogenetic studies are available. Biologically, it is a low grade malignancy [346]. A few years ago, Al-Saleem et al. described what they termed an "oncocytoma with papillary carcinoma foci". The tumor showed a positive reaction for cytokeratin 7 and trisomies of chromosome 7 and 17. Although the case was interpreted as progression of oncocytoma into carcinoma or collision tumor, it may well represent the same entity that was described by May et al. [11]. If so, we would have the cytogenetic information we lack from the original description.

Cortical adenoma

By definition it is a small lesion; the classification requires a cortical adenoma to be 5 mm or less in diameter [514]; many of these are significantly smaller, fitting into a single microscopic field of view (Fig. 4). They are composed of delicate papillary or tubular structures, lined by a single layer of small cells with inconspicuous cytoplasm and regular nuclei, analogous to cells of PapRCC type 1. Such tumors may be more frequent than generally thought: Wang et al. found adenomas in 7% of all nephrectomy specimens [575]. Adenomas are relatively frequently multiple. On very rare occasions, these multiple adenomas may reach a sufficient number to merit the designation of

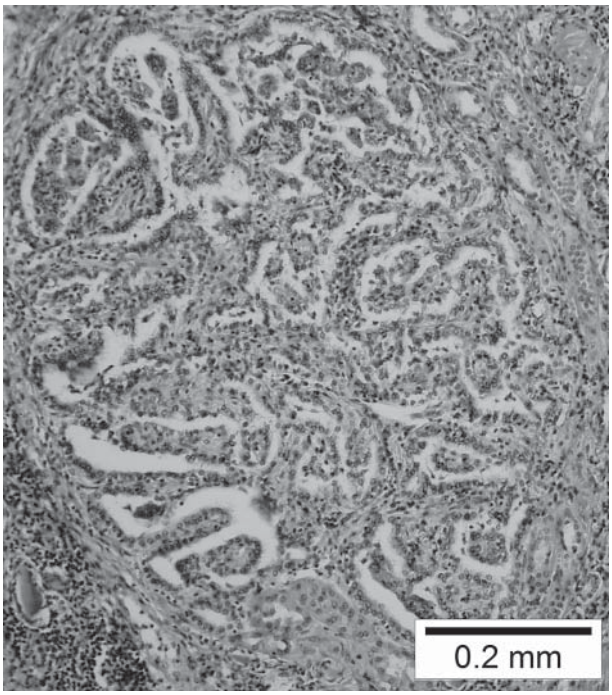

Fig. 4. Cortical adenoma. A very small nodule, entirely enclosed in this microscopic field, is composed of papillae covered with one layer of small, uniform cells with round nuclei. Hematoxylin-eosin, magnification 100x.

"adenomatosis" [419, 525]. However, on reading older reports, one has to bear in mind that the definition of adenoma changed over time and many lesions called so in the past would be now regarded as carcinomas. Presently, we never consider a clear cell tumor an adenoma, whatever its size may be. Speaking about the tumor size, it is noteworthy to observe that in the past, lesions as large as 2-3 centimeters were diagnosed as adenomas. This was due to the inability to detect small tumors using the then available imaging methods and to the only incidental availability of mostly autopsy material originating from such tumors. This practice should be long abandoned, stated that we exclude specific rare lesions, such as metanephric adenomas.

Metanephric adenoma

Metanephric adenomas (MA) are rare lesions very distinct from cortical adenomas discussed above. Certainly they are larger, with diameters measured in centimeters, thus clinically they are thought to be carcinomas. MA are more frequent in women, their symptoms are similar to other renal tumors, although polycythemia appears to be quite frequent [112]. On histology, the lesion is composed of tiny acini of small cells with scarce cytoplasm and homogeneous looking nuclei. These acini lie in a acellular, hyaline stroma. Areas with papillary or cystic arrangement of cells may be also found. Calcifications are frequent [112, 150]. On cytogenetic examination, it is possible to exclude typical changes of renal carcinomas, such as 3p deletions, chromosome 7 and 17 trisomy. Also there are no 11p and 16q deletions seen in nephroblastoma [455].

Differential diagnosis may be difficult. In particular, discrimination between MA and PapRCC or (in a small tumor) cortical adenoma may be challenging. Useful immunohistochemical stains include positive reaction for CD57; EMA and cytokeratin 7 stains are negative. Although these stains are not completely constant among PapRCC, the negativity is more likely in type 2 tumors, while MA will be rather difficult to differentiate from type 1 carcinoma, especially the solid variant [112, 338, 455, 505]. Another differential diagnosis is epithelial type of nephroblastoma [112].

Oncocytoma

Renal oncocytoma (RO) is the most frequent benign renal epithelial tumor in surgical series. Some authors report RO occurring with an increasing frequency; however, this is not confirmed in all series [13, 136, 318]. In general, tumors composed exclusively or in large part of oncocytes are known to appear especially in the thyroid; however, similar tumors are found in other organs, including the salivary glands, pancreas, parathyroid or hypophysis. Such tumors share a similar cytologic picture, although not the architecture or biology. In the kidney, oncocytoma was described in the forties, but recognized as a separate entity by Klein several years later [270]. RO is often an asymptomatic tumor and is usually incidentally detected although it is not very small, being several (3-6) centimeters in diameter. Larger lesions are also reported; in most recent series, smaller lesions are seen, what is a consequence of improved imaging techniques. If any symptoms are present, they are not specific and appear identical to other renal tumors [20, 427]. In 13% RO is multifocal and in 5% bilateral [20, 427]. In many instances, it may be accompanied by other, malignant lesions in the same organ (vide supra). Grossly, RO is well delimited, the cross section is characteristically mahogany in color, but this feature

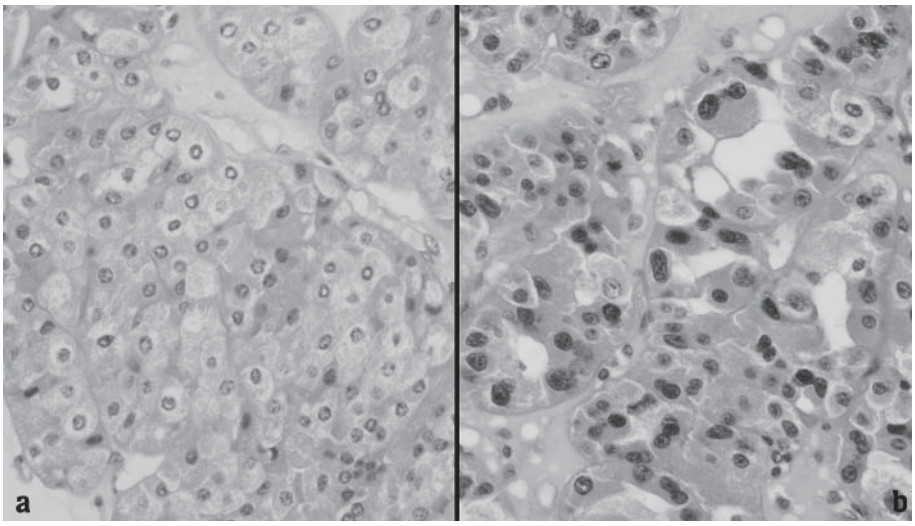

Fig. 5. Less usual cytologic variants of oncocytoma: a) clear cells, b) dark, irregular nuclei. Hematoxylin-eosin, magnification 450x.

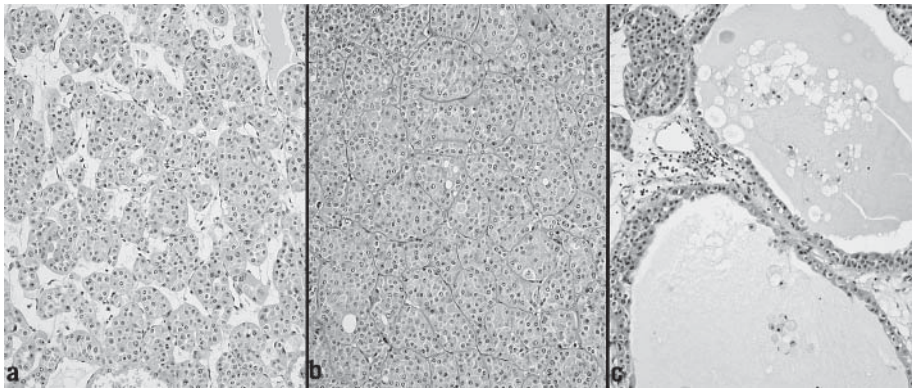

Fig. 6. The architectural patterns of oncocytoma: a) the „organoid" growth with tumor acini inside acellular stroma, b) the solid growth pattern with densely packed acini, c) sometimes small cysts are present. Hematoxylin-eosin, magnification 100x.

is often seen several hours after the cut has been done, and not on a fresh cross section. In the central part, a stellated, whitish, hyaline scar may be observed, but no necrotic foci are visible. Microscopically, RO is composed of cells with abundant, eosinophilic and granular cytoplasm. In electron microscopy, the granular cytoplasm appears to be due to a very high number of mitochondria. These densely packed mitochondria are similar to each other, spherical, with laminar cristae [145, 547]. In some cases there are foci of cells with clearer cytoplasm, but their clearing is not similar to the perinuclear "halo" typical for chromophobe RCC (Fig. 5). These clear cells are more frequent near the central scar. In the unusual variant described by Koller et al, the cytoplasm contained vacuoles, which seemed to be derived from extremely degenerated mitochondria [273]. The nuclei of RO are medium-sized, round, with regular borders and finely distributed chromatin. The nucleoli may be visible to prominent. Focally, the nuclei may be dark and irregular (Fig. 5); this should not be considered a feature of malignancy. The number of mitotic figures is very low and no abnormal mitotic figures are seen. Beside typical, large (hence "oncocytic") cells, smaller cells may be present, with less abundant, though still pinkish and granular cytoplasm and a round uniform nucleus. If these small cells predominate, the diagnosis may be less obvious [20, 427]. The growth pattern may be solid, composed of characteristic "organoid" acini, sometimes alveolar or cystic areas (Fig. 6). Although in rare cases the pseudopapillary growth pattern is observed, no true papillae should be present. Any such formations cast doubt on the diagnosis of RO and need differentiation from rare forms of PapRCC (vide supra). Between the cellular foci, paucicellular or seemingly acellular stroma is seen; the stroma has an edematous or hyaline appearance. As it has been already mentioned above, in the central part of the tumor, a hyaline scar may be found. This scar may be visualized in imaging studies, allowing for establishing a preoperative diagnosis [440]. Although at first regarded as entirely specific, is currently known to not infrequently occur within other tumors, namely RCCs [20, 145, 320, 427, 514, 539]. If a scar is detected in renal tumor imaging, some authors believe that thin needle aspiration biopsy is indicated. The diagnosis of RO would thus allow for less aggressive treatment, especially partial nephrectomy. However, other authors advise caution, as the cytology has a limited distinguishing power and a second, malignant tumor may be present. Moreover, partial nephrectomy is currently used frequently for small renal tumors, irrespectively of their histology (vide infra). In 10% of RO, capsular invasion may be detected. A less frequent and at the same time disquieting feature is renal vein invasion. Such tumors were proposed to be called "atypical oncocytoma" on the basis of uncertainty as to their entirely benign biology [20, 191, 427]. Otherwise, "atypical oncocytomas" share all the morphologic, immunohistochemical and molecular characteristics of their standard relatives. Their biology is a matter of debate, with some reports stressing their non-benign behavior, [427], while others deny any prognostic difference from the bulk of RO [214].

In general, RO is a benign tumor. It is currently thought that older descriptions of metastasizing oncocytoma are rather misdiagnosed carcinomas, especially of the types that were not known at the time [199, 314, 319, 437, 561]. In fact, this is just the impression a current-day pathologist has while looking at the photographs in these reports. Only a single description of a true metastasizing oncocytoma is said to be presented in the literature, with a biopsy-proven liver metastasis [427]. The existence of both "benign" and "malignant" oncocytomas gave origin to the practice of grading RO. This was said to have prognostic significance, because indeed metastatic spread was seen in cases with

diffusely pleomorphic, atypical nuclei. These genuine features are currently regarded rather as criteria diagnostic for other lesions, such as chromophobe carcinoma. The present practice denies any need for grading RO, regarding these tumors as uniformly benign.

On the other hand, cytogenetic data point to heterogeneity of RO. Three main groups of alterations are reported: 1) chromosome 1 and Y deletions, 2) translocations between chromosome 11 (break point at locus 11q13), and other chromosomes 3) other, heterogeneous alterations, including monosomies of chromosome 14, trisomies of chromosome 12, translocations t(13; 16), various types of loss of heterozygosity. The latter group of changes, which is the least well defined, would be at the same time the most frequent [239, 281, 431, 574]. Interestingly, nuclear genes of mitochondrial proteins are located just in chromosomes 1, 11 and 20. On the other hand, it was suggested that RO with chromosome 1 loss may be related to chromophobe carcinoma and that RO progression to chromophobe carcinoma might follow additional genetic alterations. Kovacs et al. described two cases of mosaicism with a mixture of cells with and without translocations [281]. In some publications, mtDNA deletions were reported, but this is not a constant finding [531]. Simonnet et al. reported changes in mitochondrial complex I (NADH dehydrogenase). In contrast to other renal tumors, in RO the activity of other mitochondrial enzymes was increased [500]. These alterations were present also in seemingly normal renal parenchyma in the immediate vicinity of the tumor. More recently, it was reported that RO mtDNA bears point mutations, including complex I genes. These were detected in all tumors examined [175]. It was also argued that the growth of RO might be to a greater degree dependent on apoptosis inhibition than cellular proliferation, which is low, indeed [442].

In some oncocytomas, familial clustering was noted. Weirich et al. described 18 RO patients belonging to five families [581]. Such tumors are bilateral or multiple more frequently than in the case of sporadic ones; in some families, massive, bilateral tumors occupied most of the renal parenchyma, leading to renal failure [86, 239, 531, 576]. This pathoclinical picture bears some similarity to BHD-deficient mice, where increased tubular epithelial proliferation, with hyperchromatic nuclei and eosinophilic, granular cytoplasm is seen and renal failure develops (vide infra) [35]. The biology of familial oncocytoma is, like in the case of its sporadic counterpart, entirely benign. The tumor detection is incidental, or takes place during family screening. The genetic background and mechanism remains obscure; some of the cases may be linked to Birt-Hogg-Dubé syndrome [86, 239].

Oncocytosis was also seen in a sporadic form [576]. Tickoo et al. described a quite large series, consisting of 14 cases of this rare entity [548]. The lesions detected were obviously ROs; however, chromophobe carcinomas and hybrid tumors were also seen. Such heterogeneity is analogous to the features of Birt-Hogg-Dubé syndrome; however, there was no evidence of familial clustering in these cases.

It is believed that RO differentiates towards intercalated A cells of the cortical collecting ducts [433, 515, 560]. The collecting duct origin is confirmed by immunohistochemical studies, in which RO was shown to express carbon anhydrase II and anion exchanger band 3 that are specific markers of cortical collecting ducts. Other indications of the above-mentioned RO origin are positive reactions with Dolichos biflorus and, to a minor degree, with Ulex europeus lectins [270, 284, 406, 515]. Other markers of some significance may be caveolin-1 antibody, with which ROs react much stronger than RCCs [73]. Stain for cytokeratin 7 is focal and not as strong as in some carcinomas [357, 362]. The stains for RCC antigen are usually altogether negative, while CD10 may be positive in some cases [506]. Vimentin stain, even strong, may be present in the majority of cases; however, it is only focal, with positive cells concentrating near the central scar. This is in contrast with a diffuse reaction seen in some carcinomas [213, 506]. Anti-mitochondrial antibodies would seem to be an effective RO marker; however, their performance is not as good as expected. In fact, all the tumors with abundant granular cytoplasm that enter into the differential diagnosis spectrum may contain a large number of mitochondria [1, 545]. Rampino et al. described constant expression of the Ron protooncogene (RON, MST1R, MIM 600168 [234]); this finding is in contrast with RCCs that are devoid of Ron expression. Ron protein is a tyrosine kinase of the Met family, a receptor for macrophage stimulating protein (MSP, HGF-like protein MIM 142408 [234]). In a normal kidney, Ron is constantly expressed by tubular epithelial cells; it is responsible for cellular renewal and reactivity to cellular damage. Thus, this signaling system has an analogous role to the more extensively studied HGF/HGFR. Rampino et al. believe that Ron retention in RO is a remnant of normal signaling, whereas loss of expression is an effect of molecular alteration in the course of oncogenesis. These results would be in sharp opposition to some other tumors, in which Ron signaling activation participates in cancer formation and progression [425, 442]. These interesting results were not, however, confirmed by further studies, where no significant difference in Ron expression was seen between RO and chromophobe carcinoma [422]. This seems to be a constant motif in renal tumor pathology – new methods used for definite distinction between these two tumors appear of little value if studied in details. RO has a high endogenous biotin activity leading to non-spe-

cific reactions [505, 506]. This was quoted, for example, as the reason for positive cytokeratin 14 stains obtained in some, but not other studies [89].

Chromophobe carcinoma

Chromophobe carcinoma (ChRCC) described as late as in 1985 [540], is an infrequent renal tumor. It is not an aggressive cancer, with the majority of cases limited to the kidney. On the other hand, it tends to be rather large and the rate of sarcomatoid transformation is higher than in other RCCs. The latter property has the same grim prognostic significance than in other histological types. If metastases appear in ChRCC, they will be found in the liver more often than in other histological types [8, 9, 103, 453, 541]. Grossly, the lesion is as well circumscribed as the bulk of RCCs are, the color is brown to tan to gray. On histology, ChRCC grows in a solid pattern, at times also forming tubules or ribbons. The cells are large, polygonal, with prominent cellular borders. Cytoplasm is abundant, pinkish, reticular or somewhat granular. PAS staining for glycogen is negative. Around the nucleus, a characteristic clearing ("halo") may be seen. A second cellular population is composed of smaller cells with eosinophilic, less abundant cytoplasm. The eosinophilic variant of ChRCC is composed only of these smaller cells. This variant is said to be even less aggressive than the classic type [403]. Another, rare variant described by Hes et al. showed microcystic, glandular and almost cribiform architecture, deposition of brownish pigment and calcifications, some of them in the form of psammoma bodies [215]. The nuclei of ChRCC are characteristically dark, often surprisingly irregular; the nucleoli are inconspicuous to small. Some binucleated cells are usually seen. The extensive network of thin-walled vessels typical of CCRCC is absent, but thick-walled, sometimes hyalinized vessels may be numerous [140, 516, 540, 541]. The classic stain used for confirmation of ChRCC diagnosis is colloid iron, either by Hale or Mowry method. This stain should be diffusely and strongly positive [546]. Although colloid iron stain was once regarded as very sensitive and specific, it was reported also in other renal tumors, including CCRCC, PapRCC and RO; thus, it cannot be trusted to be entirely specific [345]. Another classic diagnostic method is electron microscopy; a multitude of tiny vesicles are visualized in the cytoplasm. These vesicles vary in size, usually having the diameter of 140 to 300nm, but ranging from 100nm to 750nm. The vesicles accumulate near the nucleus, are round, oval or elongated, are usually delimited by a single-layer membrane, but sometimes the membrane may be two-layered. They were identified as invaginations of the exterior mitochondrial membrane. Contrary to earlier reports, the microvesicles are not entirely specific for ChRCC. Their another inconvenient feature is that they are friable, requiring good quality material; in particular, paraffin embedded material is unsuitable for their detection. In the eosinophilic type of ChRCC, the cytoplasm contains several mitochondria. They are varied in size and shape; both laminar and tubular cristae are present. In some cases, the mitochondria are identical to these of RO [58, 144, 145, 538, 541, 547]. Similar ultrastructural features were described in rodents` tumors caused by streptozocin; however, this is likely a casual coincidence [125]. The point of origin of ChRCC would be the intercalated B cell of the collecting duct, which shares many characteristics, including the electron microscopy structure or carbon anhydrase II expression [433, 516, 527].

On cytometry, the hypodiploid DNA pattern is detected, what is in concordance with cytogenetic studies, which show deletions or loss of heterozygosity on several chromosomes, especially 1, 2, 3, 6, 10, 13, 17, 21 [8, 65, 66, 276, 315, 486, 508]. Alterations in the mtDNA were also described; these are different from the alterations seen in RO [276].

The molecular background of ChRCC is not well known. As in the case of other renal tumors, the analysis of familial cases gives some insight. Thirty years ago, Birt, Hogg and Dubé described a familial syndrome consisting of multiple skin tumors, such as fibrofolliculoma, trichodiscoma and acrochordons [52]. Another characteristic feature is spontaneous pneumothorax due to pulmonary cysts formation. Years later, in 1993, renal tumors in Birt-Hogg-Dubé syndrome were described [473]. The renal neoplasia may be of diversified morphology, often these are ChRCC (33%). Less frequently, oncocytomas may be seen (5%). In half of the cases, the renal tumors have hybrid morphology with features of both ChRCC and RO [325, 423, 608]. Beside distinct tumors, in the renal parenchyma of BHD syndrome patients, oncocytic metaplasia may be seen. This has been interpreted as a possible precancerous lesion [423]. In the rare clear cell tumors of Birt-Hogg-Dubé syndrome, no VHL gene alterations are detected. The protein product of the gene mutated in BHD syndrome (locus 17p11.2, MIM 607273 [234]) is called folliculin. Folliculin participates in the signaling pathways related to AMP-activated kinase (AMPK) and mammalian target of rapamycin (mTOR) (Fig. 7). The exact nature of these interactions is not completely understood at the moment; however, they transmit the signals of deficiency of nutrients or ATP. Thus, the pathway may be called the "starvation pathway", analogously to the hypoxia pathway VHL/HIF/VEGF activated in CCRCC. In fact, these signaling pathways are interconnected [36, 392, 553, 554]. In mice, inactivation of the BHD gene results in increased proliferation of the epithelial cells, renal cysts formation, renal failure and death. The proliferating tubular

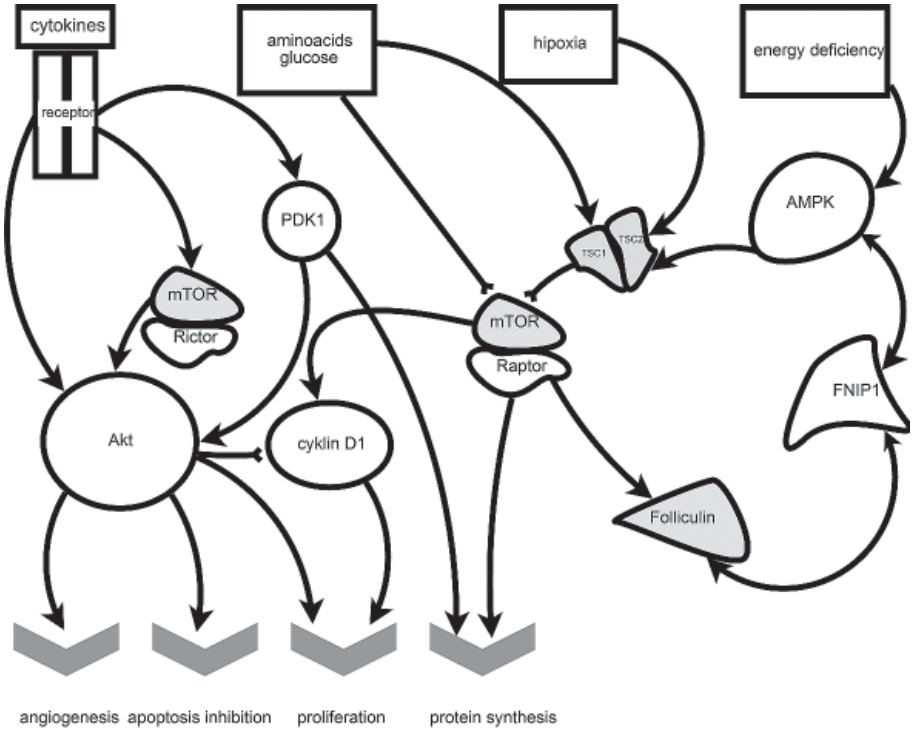

Fig 7. The mTOR pathway with the putative role of folliculin and TSC1/TSC2 complex.

epithelial cells have hyperchromatic nuclei and eosinophilic cytoplasm, somewhat analogously to the tumor morphology in BHD syndrome. This effect may be reversed by administration of rapamycin or its analogues [35]. The BHD gene mutations were detected in some spontaneous renal tumors, including some ChRCC. Thus, contrary to other renal tumor-related mutations, but analogously to the renal tumors of BHD syndrome, the BHD gene alterations are not morphologic-type specific. An alternative mechanism is the BHD gene promoter hypermethylation. This phenomenon was shown by Khoo et al. in as many as 1/3 of ChRCC [252]. The mTOR pathway may be activated in RCC independently of folliculin; in fact, in renal transplant recipients in whom rapamycin was used as an anti-rejection drug, the renal tumors (and in general all cancers) risk decreases [566]. Another hypothetical mechanism of ChRCC might depend on the increased CD117 expression [589] however, the c-Kit gene mutations are quite rare [197, 428, 429, 490]. For this reason, it is not likely that RCC patients would benefit from therapy with imatinib (Gleevec); the activity of this drug is indeed dependent on c-Kit exon 9 and 11 mutations. What is more, no difference in CD117 expression was seen between ChRCC and RO; thus, the c-Kit immunohistochemistry would be useless for differential diagnosis and it may only be employed for distinguishing ChRCC from CCRCC [316, 344, 429]. Another result of some interest in view of the pathogenesis is presented by Baiyee and Banner [37]. They detected loss of expression of MSH2, unlike the pattern of other RCCs. However, an analysis of a large series is needed before conclusions about the relationship between genome instability and ChRCC are drawn. It is noteworthy, however, that an early work by Kovacs describes genetic instability in ChRCC consisting of a tendency towards multiple chromosome breaks [276].

One of the challenging problems of renal tumor pathology is differential diagnosis between oncocytoma and chromophobe carcinoma. The practical significance of distinguishing a benign and a malignant – although low grade – tumor is obvious. Distinction between ChRCC and other, more aggressive variants also has practical significance and is difficult in some cases. The identification of suitable markers may require extensive studies. Young analyzed gene expression patterns in various renal tumors. This allowed for proposing an immunohistochemical mini-panel, consisting of the stains for β defensin, parvalbumin and vimentin. ChRCC and RO were positive for β defensin, parvalbumin, the majority of PapRCCs were positive for all three markers and CCRCC was positive for vimentin only [597]. Hornsby et al. analyzed the gene expression microarray and found that claudin-7 and claudin-8 were expressed specifically in ChRCC. On immunohistochemistry, claudin-7 was expressed in ChRCC, but not CCRCC;

however, it was also present in 25% of ROs and PapRCCs [219]. In another study, an effective distinction between ChRCC and RO was obtained, with the most contrasting expression among tight junction component genes, other intercellular junction genes and endocytosis and intracellular transport genes [469]. These genes showed high expression both in normal tubular epithelial cells and in ChRCC, but were suppressed in RO. This may be due either to different cell of origin, or loss-of-function during tumorigenesis. Although very interesting from the scientific point of view, these data have limited usefulness for a practical diagnostic purpose. Firstly, the molecular methods are not currently routinely and easily accessible in histopathologic practice as is immunohistochemistry. Secondly, the authors on purpose limited their analysis to cases which could be unambiguously assigned to RO or ChRCC category. Thus further studies are required.

All cases of both ChRCC and RO show some cells positive for the progesterone receptor, but in CCRCC all cells are negative. The pathogenetic significance of this finding is uncertain, but the progesterone receptor positivity may rule out the CCRCC variants. ChRCC is also reported to be constantly negative for the estrogen receptor, while in RO some cells may show positive reaction [344]. ChRCC is also negative for aquaporin-1, while MUC1 (EMA) is usually positive. The last marker has also a characteristic pattern of staining; contrary to the standard name of the antigen, the reaction is not membranous, but diffusely cytoplasmic. This may have some usefulness for differential diagnosis; however, cytoplasmic EMA may be also seen in other cancers, including less differentiated or sarcomatoid CCRCC [299, 362]. An even more extreme problem in differential diagnosis is presented by cases of tumors with features characteristic of both ChRCC and RO; these lesions are particularly frequent in BHD syndrome; however, they may be encountered sporadically. Abrahams et al. analyzed a series of 32 such tumors. If optical microscopy was used as the only tool, the rate of concordance between the experts was poor (κ=0.3). The most reliable features of ChRCC were distinct cell borders and hyperchromatic, irregular nuclei surrounded by a clear "halo". The most useful immunohistochemical marker in this study was parvoalbumin, with 100% specificity and over 90% sensitivity. Less effective were the stains for EMA, CD10, cytokeratin 7 and mitochondrial antigens. The Hale`s colloid iron stain was largely useless [1]. One of the most useful immunohistochemical stains employed in confirming the diagnosis of ChRCC is cytokeratin 7, which has become a kind of standard. It shows a high degree of usefulness, because it is not only positive in a truly large proportion of cases, but has a very characteristic, submembranous pattern, which is quite easy to recognize. RO shows only a weak, diffuse cytoplasmic staining, allowing for a reliable distinction [357, 505, 506]. ChRCC does also express cytokeratins 8 and 18; the stains for CD10 and RCC are usually negative [33, 298, 505, 506]. The negative CD10 and RCC stains may be of some use, if proximal tubular tumors, such as CCRCC and PapRCC are to be excluded. Kidney-specific cadherin (ksp-cadherin) is an adhesion particle present on normal distal convoluted tubular epithelial cells [493]. It is expressed in a large majority of ChRCCs and was claimed to be absent from RO [361]; however, in other reports it was found also in the later tumor and in a minority of CCRCCs and PapRCCs. Some high grade cases would even coexpress RCC antigen and ksp-cadherin [285, 493].

In view of the difficulties in distinguishing between ChRCC, RO and other tumors, some authors attempted to use quantitative pathology methods. Castren et al. were able to discern between RO and RCC based on very elemental nuclear features, including size and shape factors [75]. However, this interesting work was done in a limited material and the RCCs under study were not described in details. Flow cytometry or image analysis-based DNA-ploidy may also offer some potential for differential diagnosis. RO is DNA-diploid in these low-resolution methods, whereas ChRCC may be shown to be hypodiploid [7, 315].

Concluding the problem of differential diagnosis between RO and ChRCC, the issue may more fundamental. There is some evidence that no sharp border between the two entities exist. Although in most cases the distinction is made easily by routine staining and needs only an immunohistochemical confirmation, in a minority of cases several immunohistochemical stains are needed before making the distinction and in yet other cases, the lesion may share the morphological, immunohistochemical and possibly molecular features of both entities. As the pathogenesis of RO and ChRCC require further studies, so does their histological differential diagnosis.

Medullary carcinoma

Medullary carcinoma (MC) is a rare type of RCC, with only a few dozens of cases described so far. It has been first seen and is still detected almost exclusively in individuals with sickle cell trait or sickle cell anemia (locus 11p15.5 MIM 603903 and 141900 [234]). MC is a disease of children and young adults. It is derived from the most distal part of the collecting ducts and has a truly strong histogenetic relationship with urothelial neoplasia, although their morphology is quite dissimilar. Coexistence of both lesions was indeed reported and is not thought to be coincidental [156]. The mechanism of MC carcinogenesis

would be related to chronic renomedullary hypoxia due to the primary disease, leading to HIF activations. Although in normal cells, such signaling leads to apoptosis, if p53 inactivation is present, which appears to be an early event in MC, VEGF signaling is activated. To some degree, this pathway is analogous to the CCRCC hypoxia pathway [72, 160, 489, 522].

MC is an extremely aggressive neoplasm. All but few cases are advanced and disseminated at the time of diagnosis. The median survival is 15 weeks. The current treatment modalities seem not to alter this grim prognosis [3, 113, 198, 378, 439, 522].

Collecting duct (Bellini) carcinoma

Collecting duct carcinoma (CCC) is confused in some reports with medullary carcinoma. It is important to keep a sharp distinction between these entities, because their features are altogether dissimilar; they share only the very-distal-tubular origin and medullary location, but differ in their pathogenesis, clinical characteristics of the patients, genetics and morphologic picture [522].

In 1976, Mancilla-Jimenez observed hyperplastic and dysplastic changes in the collecting ducts in the vicinity of some renal tumors and concluded that these tumors might be derived just from the collecting duct cells [350]. Currently, it is thought that CCC originates from the chief cells of the medullary portion of the collecting duct, in contrast to the intercalated cells being the origin of RO and ChRCC [433]. CCC is a tumor of the elderly and as most of other renal cancers, it is more frequent in males. More frequently than other histological types, the lesion is symptomatic [246]. The classic location is the renal medulla or corticomedullary junction; however, locally advanced lesions may hamper proper location of the point of origin. In contrast to most renal tumors, CCC demonstrates the infiltrative pattern of growth, although this is not always grossly evident. The central location of a strongly infiltrating mass may allow for establishing the diagnosis in imaging studies. On microscopic examination, there are highly atypical cells growing in the tubular or papillary pattern in rich desmoplastic stroma. Although early descriptions underlined the papillary growth pattern, it is not the dominant feature and caution is needed if diagnosing CCC with a papillary-only architecture [76, 116, 159, 290, 404, 474]. Sarcomatoid transformation may be seen even in 30% of cases [116]. For the diagnosis, special stains are essential. On immunohistochemistry, the characteristic feature is co-expression of high- and low-molecular weight cytokeratins and positive staining with Ulex europeus lectin [76, 130, 290, 459, 474]. EMA expression is variable, although it is one of the distal tubular and collecting duct lineage markers [311]. In cytogenetic studies, no specific pattern was described. In most reports, complex karyotype alterations were described, including monosomies of chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22 and trisomies of chromosomes 7, 12, 17, 20 observed with varying frequency. The most constant change would be 1q32 deletion [188, 511]. Cytogenetics may exclude alterations that are of diagnostic importance for other forms of RCC [76, 459]. The molecular pathogenesis of CCC is not known. The described alterations include HER2 amplification, overexpression of bcl-2, p53 mutations, overexpression of HGF-R, loss of CD117, FEZ1 or FHIT [83, 248, 488, 568]. The etiology of CCC continues to be equally unexplained. Sacura et al. described a case of combined CCC and CCRCC in the contralateral kidney in the course of acquired polycystic kidney disease with a 20-year history of hemodialysis [477]. However, it is only a single observation. CCC is often observed together with extrarenal tumors, both synchronously or metachronously [78]. A few years ago we encountered a case of CCC and pulmonary adenocarcinoma [398].

Clinically, CCC is a highly malignant lesion, usually advanced at diagnosis. Lymph node and distal metastases and renal vein infiltration are frequent [78, 159]. Chemical treatment does not trigger any response and surgery remains the only method available. The average survival is only 2 years [129, 159, 251, 398, 459, 477]. In contrast, recently, Karakiewicz et al. thoroughly analyzed a large series of CCC cases and claimed that the prognosis was no different than in other renal cancers of the same grade and stage [246]. These data, however, certainly require confirmation by further studies.

Tubulocystic carcinoma

Among the lesions thought to share the collecting ducts differentiation, there are also low grade tumors ("low grade collecting duct carcinomas"); their relationship with collecting ducts has been negated recently, however. Their histogenesis, place in the classification and even their existence is not fully established; these tumors are not included in the WHO system. Currently, these lesions are called tubulocystic carcinomas (TCRCC), a name bearing no histogenetic association. As most of RCCs, they are more frequent in males; the age of the patients is quite variable. In some series, coexistence of PapRCC and cortical adenoma was seen. TCRCC is usually small, with an average diameter of 3 cm, well delimited, usually stage pT1. The prognosis seems to be favorable; the single aggressive cases are combined with other histological types. The cysts giving the lesion its name are seen grossly, giving the picture of "Swiss cheese" or sponge. Microscopically, the lesion is composed of small tubules and larger cysts, separated by

scanty fibrous tissue. The epithelium lining the cysts and tubules may be flattened, cylindrical or hobnailed. The cells have pinkish cytoplasm, uniform round to oval nuclei. The nucleoli are prominent, at least focally. Immunohistochemically, TCRCC is positive for cytokeratin 8, 18, 19 and focally 7 and 34βE12, CD10, AMACR, parvalbumin. Electron microscopy shows conflicting features, with brush border, short microvilli and cellular membrane invagination. TCRCC is thus said to share the proximal tubular and intercalated collecting duct differentiation [34, 140, 340, 341, 479, 591]. Yang et al. found a gene expression pattern similar to that of PapRCC. In cytogenetic analysis, trisomy of chromosome 17, but not 7, was found [591].

Mucinous tubular and spindle cell carcinoma of the kidney

This is a new entity, described in the nineties only; it was included in the last WHO classification, but remains a challenge for less-experienced pathologists. Previously, these lesions were clustered with papillary or unclassified carcinomas or metanephric adenomas. A highly clinically important discrimination is between the above entity and sarcomatoid tumors [140,148, 149, 157, 168].

In contrast to more conventional renal cancers, mucinous tubular and spindle cell carcinoma is much more frequent in women (the female: male ratio of 3:1). The patients` age is quite varied (19-81 years) [30, 61, 148, 149, 168, 405, 494].

Its histological structure is quite characteristic and dissimilar to other lesions. There are areas composed of tubules of small cuboid cells with small and uniform, round nuclei; the other component is composed of spindled cells with equally small, uniform and monomorphic nuclei. The number of mitotic figures is very small. In the stroma, PAS-positive and Alcian blue positive mucinous substance is present [30, 61, 140, 148, 149, 157, 168, 289, 441]. In the material of Department of Pathomorphology, there are four such cases, three of which were reported [399].

Cytogenetic and molecular features were examined in few cases only. Ferlicot et al. described a case with extensive chromosomal abnormalities, including deletions of chromosomes 1, 4, 6, 11, 8, 13, 14, 15, 18, and another with deletions of chromosomes 1, 6, 11, 14, 22 and trisomy of chromosome 15 [148, 149]. Brandal et al. observed the hypodiploid karyotype in two cases and hypertriploid in one case [61]. They detected amplifications of chromosomes 10, 16, 17, 19, 20 and 21 and loss of genetic material from chromosomes 8, 9 and 13. Rakozy reported deletions of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, 22 and X [441]. Such a chromosome-loss genotype is similar to that of chromophobe carcinoma. In our material, we have seen loss of chromosome 1 and amplification of chromosomes 7 and 17 [399]. Also the immunohistochemistry results are not completely concordant. In particular, the differentiation pattern of mucinous tubular and spindle cell carcinoma remains a matter of controversy. Some authors reported distal tubular differentiation [30, 148, 149, 289], but Brandal et al. observed both proximal and distal tubular markers [61], and Shen et al. described mainly proximal tubular markers [494]. Paner et al. suggested immunohistochemical similarity to papillary carcinoma [413], but Rakozy et al. believed that mucinous tubular and spindle cell carcinoma originate from the collecting ducts [441]. Other authors suggested the origin from Henle`s loop epithelium [285, 579]. Another interesting feature is positive staining for neuroendocrine markers, such as neuron-specific enolase, chromogranin, synaptophysin, CD57. In electron microscopy, neurosecretory granules were detected [237, 289, 399].

The prognosis in mucinous tubular and spindle cell carcinoma is favorable, with the surgical resection being curative in almost all cases [30, 148, 149, 168, 494].

Post-neuroblastoma renal cell carcinoma

In the survivors of neuroblastoma treated in early childhood, an increased risk of RCC is observed. The second tumor appears usually in early adulthood [147]. The tumor has distinct morphology: it is composed of large cells with oncocytic cytoplasm and high-grade nuclei with huge nucleoli, growing in the diffuse or papillary pattern. Psammoma bodies are often seen. The nature of the link between the two tumors remains unclear; however, although at first RCC was thought to be a consequence of radiotherapy, adjuvant treatment seems unlikely as the sole responsible factor [139, 140].

Sarcomatoid carcinoma

Sarcomatoid carcinomas were classified as a separate entity until the nineties [6, 383]; however, they are currently regarded as the common pathway of dedifferentiation and whenever possible, should be clustered with their cancers of origin. Chromophobe and collecting duct carcinomas are overrepresented among tumors undergoing sarcomatoid transformation [9, 82, 116, 119, 140].

Sarcomatoid carcinomas are usually large and advanced and sarcomatoid features are one of the unquestionable factors of a poor prognosis [9, 82, 116, 119]. In cytogenetic studies, the same alterations of the original cancer are to be expected, together with superimposed multiple aberrations that lead to DNA aneuploidy [95, 327, 328, 329, 330]. The very process of dedifferentiation may depend on

novel p53 gene mutations, as in some dedifferentiated tumors in other locations [395].

In rare cases, only the sarcomatoid component is visible, requiring differential diagnosis with a true renal sarcoma. In immunohistochemistry, epithelial markers are detectable; of these, AE1/AE3 cytokeratin is particularly helpful. Reactions for vimentin and actin may also be positive [9, 119, 126].

Unclassified renal cell carcinoma

Tumors that do not fit into any of the defined categories are clumped together under the heading of unclassified renal cell carcinoma (URCC). Tumors with divergent differentiation, largely necrotic tumors and carcinomas with sarcomatoid-only histology, as well as lesions that do not fit into the existing categories (and may be recognized in the future as representing new entities) are also included. A special case is constituted by papillary cancers with clear cells, which truly may represent variants of CCRCC (vide supra) [167, 478]. URCCs are often huge and high-stage; as may be expected, the prognosis is poor. Some evidence exists that the surgical-only approach is of a limited benefit for the patient. According to Zisman et al, the addition of immunotherapy may significantly improve the survival [140, 613].

Renal carcinoid and other neuroendocrine tumors

Renal carcinoid is very rare and described only in single case reports or short series [201, 444]. Metastatic carcinoid may be even less frequent, with only a single description with a primary focus in the lung [529]. Tumor morphology is analogous to well differentiated neuroendocrine tumors in other organs. Interestingly, carcinoids were repeatedly reported in horseshoe kidney. In general, congenital renal defects, including horseshoe kidney, increase the frequency of any renal tumor [331]. In some cases, renal carcinoids may be a component of a mature teratoma [596].

Less differentiated neuroendocrine carcinomas may also be found in the kidney. These are typically composed of round to elongated cells forming ribbons and nests. The nuclei have "salt and pepper" chromatin and sparse cytoplasm. On immunohistochemistry, neuroendocrine markers, such as chromogranin, enolase, synaptophysin and CD56 are (variably) positive and cytokeratins show a characteristic, dot-like pattern. As in other locations, poorly differentiated neuroendocrine carcinomas are aggressive tumors with a poor prognosis [140]. In some cases, metastatic small cell neuroendocrine carcinomas, especially arising from the lung, have to be ruled out. In the files of the Krakow Department of Pathomorphology, there is a single autopsy case of pulmonary small cell carcinoma metastasizing into a multilocular cystic clear cell carcinoma (unpublished observation).

As it has been mentioned above, mucinous tubular and spindle cell carcinoma may belong here, as it express neuroendocrine markers.

Angiomyolipoma

Angiomyolipoma (AML) is not a frequent entity in surgical material, but it may be clinically silent, left undetected and untreated. In one unselected autopsy series it was reported in as many as 8% of all cases. Even if these figures are exaggerated, certainly AML is the most frequent mesenchymal renal tumor [363, 530].

Some AMLs are seen in patients with tuberous sclerosis complex. Tuberous sclerosis is an autosomal dominant disease; however, the majority of cases are caused by new mutations [86]. Such mutations involve the hamartin gene (TSC1, locus 9q34, MIM 605284 [234]) or the tuberin gene (TSC2, locus 16p13.3, MIM 191092 [234]); other loci thought to be involved in the pathogenesis of tuberous sclerosis were not confirmed [234]. The protein products of TSC1 and TSC2 act together forming a complex that inhibits cellular growth (Fig. 7), affecting the mammalian target of the rapamycin (mTOR) pathway [370]. Rats with TSC2 inactivation develop spontaneous renal cancers composed of chromophil cells. These tumors are partially cystic, entirely solid or tubulopapillary [326]. In human tuberous sclerosis, renal carcinoma may also be seen. Histologically, these are usually CCRCCs, but PapRCC, ChRCC and RO may be encountered as well. It was recently realized that some of the RCCs known from older reports are truly epithelioid AMLs; the distinction on the basis of optical microscopy only may be extremely difficult [233, 424]. The mTOR pathway does participate in spontaneous CCRCC development [466]. Sporadic AMLs share a similar pathogenesis with the tuberous sclerosis cases: they are due to mutations or loss of heterozygosity of TSC2 locus, rarely TSC1 [352, 353].

The histogenesis of AML is not fully established. For a long time, it was thought to be a hamartoma (Fig. 8). This opinion was due to the link with tuberous sclerosis and the unusual, "mixed" histological structure. However, a body of evidence was collected in the nineties, showing chromosomal rearrangements and clonal growth both in familial and sporadic cases [117, 187, 249]. A very exciting concept is that of PEComas: tumors thought to be derived from the so called perivascular epithelioid cells; beside AMLs, they also include pulmonary clear cell "sugar" tumors, lymphangiomyomatosis and rare lesions composed of smooth muscle-like cells. Most of them are benign; however, some

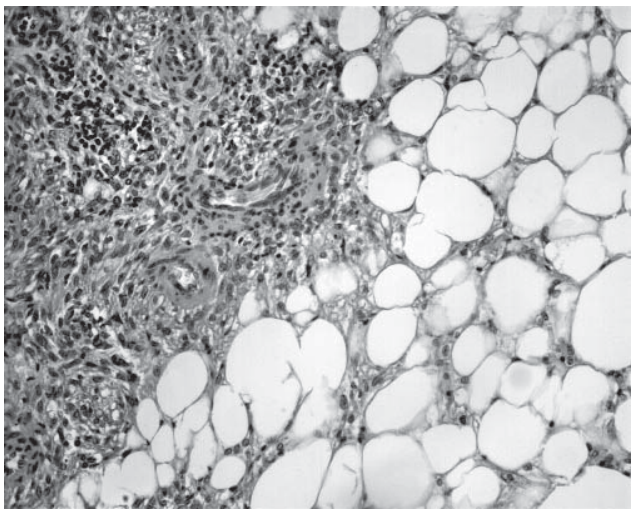

Fig 8. An angiomyolipoma. Smooth muscle-like cells are seen on the left with some thick-walled vessel towards the center; on the right, adipocyte-like cells. With such classic picture, the hamartomatous nature of the lesion appears (wrongly) obvious. Hematoxylin-eosin, magnification 95x.

poorly differentiated variants were described to be malignant and even considerably aggressive [55, 218]. A characteristic common feature of PEComas is co-expression of smooth muscle and melanocytic markers. They were also described to share alterations of the TSC2 gene and mTOR pathway activation [412]. Not all the researchers do believe in the PEComa concept, however. No normal counterpart of epithelioid perivascular cell was found so far and, consequently, there is no evidence for a common origin of all PEComas.

Single cases of non-AML PEComas were described in the kidney and renal capsule [384]. Some of these tumors may have been diagnosed previously as smooth muscle tumors, since expression of melanocytic markers was described in such lesions [57]. A peculiar feature of PEComas, including AMLs, is the almost universal presence of CD1a, a maker of such immunologically active cells as the Langerhans cells or thymocytes. It is unknown whether CD1a expression is indeed a feature of perivascular epithelioid cell or it is an aberrant feature acquired in oncogenesis [2].

Clinically, AML is usually asymptomatic, but occasionally may present with chronic renal failure or hemorrhage. This is especially true for the largest tumors. Microscopically, AMLs are composed, in varying proportions, of adipocytes and smooth muscle cells. The latter may be more spindled or more epithelioid, often, with pleomorphic nuclei. The vessels, also present in varying numbers, are thick -walled and often hyalinized (Fig. 8). A high fat content may allow for a proper diagnosis by imaging methods, although caution is needed, as focal but still radiologically detectable fat tissue may be present in RCC and RO [218, 258]. Immunohistochemically, coexpression of smooth muscle and melanocytic markers is seen. Of the later, the most frequently used is HMB-45; no S-100 protein is detected. Interestingly, unlike true adipocytes, these of AML are also negative for S-100. The CD117 stain may be positive. Some tumor cells may contain pigment [212, 348, 349, 352, 502]. Beside the classic type, the epithelioid type is recognized. It is composed of epithelioid-looking cells, with the usual smooth muscle-melanocytic phenotype typical of AML. Pleomorphic nuclei with prominent nucleoli are typical, as well as multinucleated cells. The nuclear-cytoplasmic ratio is, however, rather low. Differentiation from RCC requires the use of immunohistochemistry. Electron microscopy excludes the presence of any true epithelial differentiation, while electron dense granules are seen. In genetic studies, loss of heterozygosity of the TSC2 gene is seen, at least in a portion of cases [90, 352]. A sclerosing variant was recently reported, containing areas of hyalinized fibrous tissue [359]. Another peculiar rare variant is oncocytic AML. It is composed of smooth muscle-like cells, but lacks pleomorphism of the epithelioid AML [351, 502]. A further important but rare feature of AML is its malignant, sarcomatoid transformation. In these cases, a spindle cell, highly pleomorphic, leiomyosarcoma-like component is seen [90, 154, 353]. It may be difficult to answer whether a more conventional AML is entirely benign, due to difficult differentiation between multifocal development and secondary deposits. However, the cellular pleomorphism is not thought to constitute evidence of malignant behavior, nor is crossing the capsule, renal vein infiltration, vena cava invasion, or even the presence of tumor deposits in the lymph nodes. It was suggested that the epithelioid variant of AML should be regarded at least potentially malignant, although lesions with a low mitotic activity seem to follow a benign clinical course [90, 154, 352].

Renal epithelial and stromal tumor

Renal epithelial and stromal tumor (REST) is a new name proposed by Turbiner et al. for a group of renal tumors encountered in adults and composed of connective tissue and varying in sized spaces lined by epithelial cells [374, 558]. Although the name is brand-new, some of the entities are not and were previously known as cystic nephromas, mixed epithelial and stromal tumors and renal pelvic hamartomas. Though they were thought in the past to be related to congenital mesoblastic nephromas, this seems now unlikely. Similar lesions in pediatric population might be, however, related to cystic, partially differentiated nephroblastoma. REST is significantly more frequent in women,

usually medium-aged or perimenopausal, although tumors are described also in males. The latter may be related to diethylstilbestrol administration for prostatic carcinoma. In females, a history of hormonal contraception or hormonal replacement therapy is frequent. Single cases were familial or bilateral. The epidemiologic and morphological features resemble certain cystic tumors of the pancreas, bile ducts and retroperitoneum – and certainly the ovary. The histogenesis of these tumors – possibly common – is unclear; they might be derived from rests of undifferentiated fetal mesenchyma, or gonadal rests separated in the ontogenesis. RESTs may occasionally coexist with other renal tumors, both benign and malignant.

Microscopically, the epithelial component is flattened, cuboidal, cylindrical or composed of hobnail cells. Some cells may be ciliated. The mesenchymal component is variegated, from fibrous and paucicellular to composed of densely packed spindle cells, very similar to ovarian stroma (Fig. 9). Denser stroma is characteristically concentrated around glandular spaces. Individual tumors diagnosed under the rubric of REST differ mainly in the relationship between the stromal and epithelial component and the amount of stroma. In cystic nephroma, the connective tissue septa are thin, never exceeding 5 mm in thickness. In mixed epithelial and stromal tumors, there is a rich mesenchymal component, including entirely solid areas. Some of the lesions with intermediate features are difficult to categorize. It was suggested that progressive fibrosis and scarring might cause transition between cystic nephroma and mixed epithelial and stromal tumors [558]. A special variant was also described, containing abundant adipocytes. In these cases, misdiagnosis of the tumor as angiomyolipoma, both in imaging studies and in histology, is likely; however, RESTs do not express melanocytic markers diagnostic for AML [501].

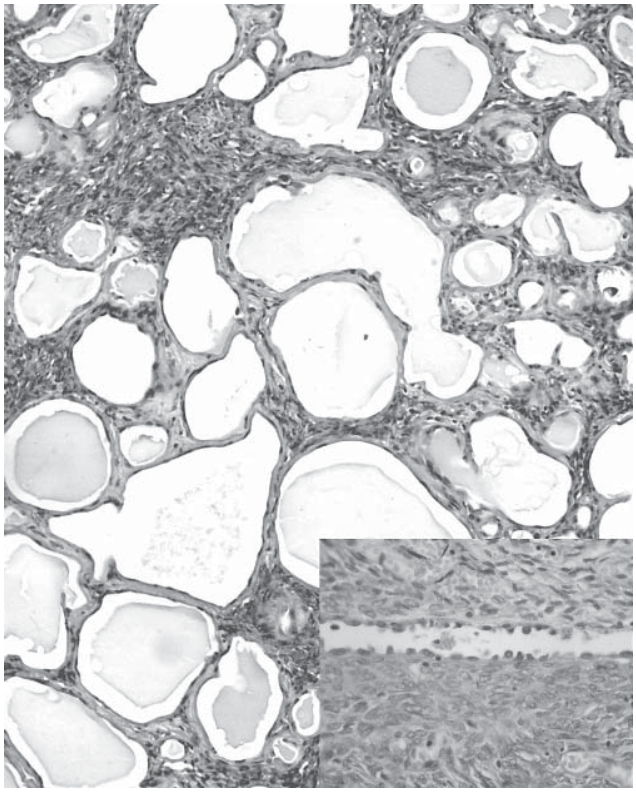

Fig 9. A renal epithelial and stromal tumor. Hematoxylin and eosin, magnification 95x. Insert 200x.

Immunohistochemically, the usual epithelial markers are positive in the epithelial lining and the spindle cells are positive for vimentin, desmin, α-inhibin, calretinin and CD34. In view of the epidemiologic link to hormonal derangements, the expression of estrogen and progesterone receptors in both components of REST is intriguing [4, 5, 98, 294, 558]. REST is a benign lesion and surgery is curative: however, sarcomatoid transformation was present in single cases. Various patterns of differentiation were described in these cases: synovial, rhabdomyoblastic, chondroblastic, as well as undifferentiated sarcoma. Sarcomatoid differentiation of REST is associated with a grim prognosis [236, 386, 521, 593]. A case of clear cell carcinoma originating in a cystic nephroma was also described [401].

Renomedullary interstitial cell tumor

Renomedullary interstitial cell tumor (RMICT) is a small, asymptomatic nodule, usually found at autopsy or incidentally in surgical specimens resected for other reasons. If carefully sought, they appear quite frequent, even in 25% of all postmortem examinations [585]. In our routine autopsy material, RMICTs were present in 5% of cases, but no special search for these lesions was possible in retrospective material [282]. Larger tumors of this type, symptomatic, detectable in imaging studies and requiring specific surgical treatment are extremely rare. Older cases, described before the advent of immunohistochemistry, are difficult to accept as credible. Lopes et al. reported another kind of a significantly larger renal fibroma located in the cortex [333, 342].

Grossly, a whitish spot of few millimeters is seen in the medullary portion of the kidney. Microscopically, there is paucicellular, hyalinized connective tissue, containing some collagen fibers, with embedded delicate, spindled or stellated cells (Fig. 10) [101, 140, 396, 434, 585].

Juxtaglomerular cell tumor (reninoma)

Juxstaglomerular cell tumor (JGCT) is definitely rare, with around 100 described cases. The usual presentation is arterial hypertension due to renin overproduction and angiotensin axis activation. Hypertension is often severe and

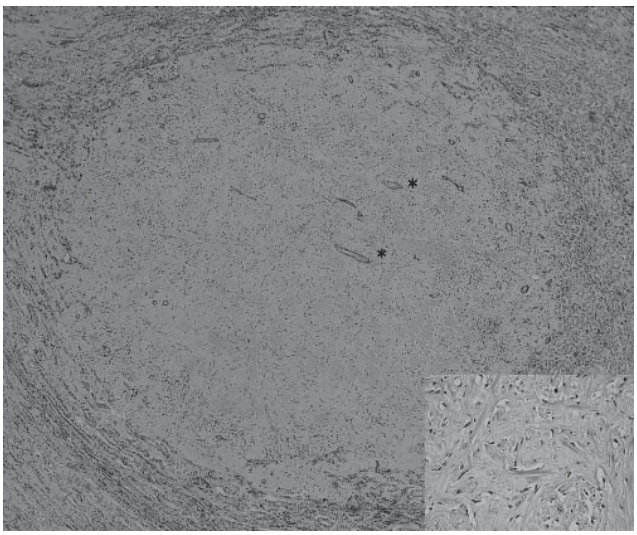

Fig 10. A renomedullary interstitial cell tumor. Normal tubules embedded into the lesion (*). Hematoxylin and eosin, magnification 2.5x. Insert magnification 240x.

resistant to pharmacological treatment. JGCT is twice as frequent in females as in males, the usual age at presentation being in the 2nd or 3rd decade of life [60].

Histologically, JGCT is composed of densely packed, round, polygonal or elongated cells; focally, microalveoli are formed by edematous stroma. Immunohistochemically, positive staining for CD34, vimentin and CD117 are seen. Smooth muscle actin may be positive focally. The stains for CD31, cytokeratins are negative. The rich vascular network is composed of variously sized vessels and may be similar to hemangiopericytoma. Significant thickening of the vessel walls would be due to the renin action. In electron microscopy, JGCT shows electron dense granules and rhomboid crystalloids containing renin. The latter are pathognomonic for the lesion [60, 140, 254, 256, 354]. Clonal chromosomal alterations were described, including chromosome 10 amplifications and deletions of chromosome 9, 11q and X [60, 70]. Although a single case of metastasizing JGCT was described, the behavior of the tumor is usually benign [134]. No standard treatment modality is established, but at least a careful postoperative follow-up is needed [261].

Other mesenchymal tumors

Other mesenchymal tumors were sporadically described in the kidney. When dealing with such tumors, it is necessary to exclude sarcomatoid carcinoma, a more likely diagnosis. For this purpose, several sections have to be taken and ancillary methods used, especially immunohistochemistry [119]. The most frequent renal sarcoma is leiomyosarcoma, followed by liposarcoma and rhabdomyosarcoma [132, 358, 410, 570]. Also synovial sarcomas, fibrosarcomas, hemangiopericytomas, angiosarcomas, PNETs and ectomesenchymomas were described. These lesions are known from single reports only and seem not to differ from analogous tumors in other locations [10, 42, 472, 542, 544, 569]. Bonib et al. reported frequent HMB-45 expression in putative renal leiomyomas; this observation may cast doubt on proper classification of these cases [57]. Several cavernous and capillary hemangiomas were described; they may be even more frequent, as they seem to be asymptomatic and are usually incidentally detected. Dense and irregular vascular network seen in imaging studies may make the distinction from carcinoma difficult. In other cases, however, nephron-sparing surgery should be possible [109, 195, 224, 400]. Mature teratoma, also in the form of a dermoid cyst, was described in the kidney; single cases of malignancy arising from a teratoma were reported [185, 393].

Hematogenous malignancies

Secondary renal involvement in the course of lymphomas and leukemias may be present in as many as 1/2 of cases; however, primary renal lymphomas are rare. The etiology is not known. Morphologically, the majority of renal lymphomas are diffuse large B-cell type [153, 192, 594]. Marginal zone MALT type lymphomas may also be seen in the kidney [173]. In contrast to other locations, no relationship with chronic inflammatory or immunologic process was reported. Interestingly, in the series described by Ferry et al, in 50% of cases other cancers coexisted with primary renal lymphomas; these were colorectal and prostatic carcinomas, as well as other lymphomas [153].

Pediatric type tumors

Pediatric renal cancers, wholly separate from the entities listed above, are not discussed here in detail. These lesions may be occasionally seen in adults, however, and have to be taken into account in differential diagnosis of unusual morphology. The most important histological forms are nephroblastoma, mesoblastic nephroma, clear cell sarcoma, rhabdoid tumor, cystic partial differentiated nephroblastoma, ossifying renal tumor and metanephric stromal tumor. Metanephric adenoma (vide supra) is also related to these entities [22, 54, 564]. The prognosis for malignant lesions is usually worse than in children [41, 537]. The most frequent is nephroblastoma, although other lesions, such as clear cell sarcomas or rhabdoid tumors, may be occasionally seen [335, 518]. A case of renal clear sarcoma was described by the present authors a few years ago; the clinical course was unfavorable [91]. The relationship of adult and pediatric rhabdoid tumor was questioned;

however, molecular analysis shows that all tumors of rhabdoid morphology share the same deletions in locus 22q11.2 containing the SMARCB1 gene (SNF5/INI1, MIM 601607 [234, 426]).

On the other hand, RCC may be seen also in pediatric population, although it is rare, accounting for <7% of renal cancers observed in individuals <21 years [443, 452]. In older series, the similarity to adult tumors was emphasized [291]; however, in all probability this is not the case. The reason for the discrepancy lies in older classification systems that blurred the differences between diagnostic categories. In children, papillary carcinomas and unusual histological types are overrepresented. Only in von Hippel-Lindau disease are pediatric clear cell carcinomas frequent [452]. Interestingly, the sex ratio is different as compared to adults, with a distinct female predominance [291, 452]. Pediatric RCCs are more likely to be due to familial factors. The most intensely studied genetic substratum is germline Xp11 translocation. This leads to creation of the fusion gene composed of the transcription factor TFE3 (MIM 314310 [234]) and other genes. This translocation may be the source of a subset of RCCs in adults as well [24]. The morphologic picture of these tumors includes polygonal cells with clear cytoplasm, growing in papillary formations. Psammoma bodies are frequently seen [140, 452]. Another molecular mechanism involves t(6;11) translocation. This translocation creates the chimeric gene ALPHA-TFEB (MIM 600744 [234]). These tumors resemble to some extent conventional CCRCCs; the microscopic picture includes solid growth of large cells with clear or eosinophilic cytoplasm and collections of smaller cells with Call-Exner-like formations. Their peculiar immunohistochemical features include lack of epithelial markers, with expression of melanocytic makers instead. Obviously, this makes the distinction from epithelioid AML very difficult, although the genetic background is different. On the other hand, Hes suggested a close relationship between these entities [23, 114, 212, 286].

Urothelial and related renal pelvis tumors

Urothelial tumors (UT) have the structure analogous to that of the lower urinary tract. Interestingly and in contrast to RCC, there is no increase in incidence [85, 243, 414, 460]. In Hereditary Nonpolyposis Colorectal Cancer (Lynch II) syndrome, UT of the renal pelvis is seen in 2-9% of patients [86, 470]. The issue of classification of urothelial tumors is, similarly as in the case of bladder carcinomas, somewhat controversial. The ISUP system was, however, successfully applied and may give more consistent results than the 1973 WHO system [177, 217].

Squamous cell carcinoma may constitute 8% of renal pelvis tumors. It is seen even more frequently in coexistence with urothelial carcinoma. The frequency is increased by chronic pyelonephritis and nephrolithiasis leading to squamous cell metaplasia [137, 317].

Few cases of lymphoepithelioma were described. The microscopic structure is the same as in other, more common locations; however, no pathogenic link with the Epstein-Barr virus was described. The tumor is aggressive, but a total resection seems to be effective in controlling the disease [96, 164, 196].

In individual cases, distinction between poorly differentiated variants of RCC and UT may be difficult. Immunohistochemistry for CK5/6, CK17 and vimentin may be of some use in such cases [505]. The stain for CD10 antigen may be positive in 50% of cases and is an unfavorable prognostic sign [298].

Metastatic tumors

Symptomatic renal metastases are very rare; most of secondary renal cancers are detected at post mortem examination [87, 204, 267, 310, 571]. In the series of Choyke et al., there were squamous cell bronchial carcinomas (7 cases), colorectal adenocarcinomas (6), melanomas (4), breast carcinomas (2), uterine stromal sarcomas (2), and single cases of other cancers [87]. In Chassagne et al. series, 7 of 9 primary sites were pulmonary [79]. In the material presented by Sanchez-Ortiz et al., the most frequent group of solid tumors metastasizing to the kidney were breast and pulmonary carcinomas (13 cases each), colorectal carcinomas (11), melanomas (8), prostatic adenocarcinomas (6), head and neck carcinomas (5), pancreatic carcinomas (5), esophageal carcinomas (3), ovarian carcinomas (2), as well as various sarcomas and testicular tumors [480]. Metastatic renal tumors are usually small and multiple, although they may present as a single large lesion, requiring distinction from primary cancer. Colorectal carcinoma indeed tends to show this gross pattern of growth [87, 385, 408].

Pseudoneoplastic lesions

A rare "inflammatory pseudotumor" (IP) is composed of polyclonal lymphocytes and plasma cells, macrophages and myofibroblasts. IP is difficult to diagnose; especially challenging is the preoperative recognition and the usual clinical diagnosis is just renal cancer [50, 176, 230, 387]. Single cases of Castelman`s disease were also described to involve the kidney [205]. A relatively frequent "pseudotumor" is composed of collections of mature adrenal cortex and accordingly called "adrenal rest tumor" (ART). ART is interesting, as it may constitute a considerable diagnostic challenge for the less experienced, since it shows similarity to well differentiated CCRCC. Also the existence of renal

ART led Virchow and Gravitz to their erroneous histogenetic considerations. We described two peculiar cases of ARTs. One case consisted of a tiny nodule accompanying two cancers – one CCRCC and one PapRCC [397]. The other case consisted of a lesion grossly thought to be a simple cyst. In the fibrous wall, foci of corticoadrenal tissue were embedded [526].

Multifocal renal cell carcinoma and multiple renal tumors

The problem of multifocal RCC and the coexistence of RCC with other tumors in the same kidney are becoming increasingly important in the same way that partial nephrectomy becomes a standard procedure [430]. The most frequent observation is the coexistence of RCC with RO, which may be seen in 7-22% of all RO cases. Angiomyolipoma at times also coexists with RCC. If two histological types of RCC are seen in the same organ, one of these is usually PapRCC. Of multiple renal tumors, as much as 30% of secondary lesions may be missed in preoperative imaging studies [446]. Clear cell carcinoma accompanied by urothelial carcinoma is quite rare, with only 23 documented cases [203]. The coexistence of CCRCC and collecting duct carcinoma was also reported [32]. Rare, although not exceptional is the occurrence of three or more renal primary tumors [397].

The frequency of multifocal CCRCC is estimated as 7-25% [238]. These tumors are thought to share the same clonal origin and should be regarded as intrarenal metastases and not truly multifocal primaries [216, 238]. Kovacs observed differences in the 3p mutation pattern between typical and multifocal CCRCC; however, this finding was not further studied [279]. On the other hand, multifocal PapRCC may be seen in over 25% of cases, and these lesions are almost always independent clonal growths [235, 368].

Prognostic Factors

In the last 30 years, significant progress was achieved in RCC management. The cure rate was approximately 52% in the period of 1974-76, approximately 56% between 1983 and 1985, and increased to 65% in the 1995-2002 period [15, 414]. A slow but evident progress is thus seen and we should observe further progress in the years to come. Several factors influencing the survival are considered; the most established are obviously tumor stage, type and grade. As in the case of other malignancies, much effort is needed to estimate the prognosis of an individual patient [166, 356].

According to most, but not all studies, the RCC histologic type significantly affects the survival. In the analysis of Amin et al., the 5-year survival rate was 100% for ChRCC, 86% for PapRCC, 76% for CCRCC, but only 24% for unclassified carcinoma [18]. Few studies negate the significance of histologic type either in general [255, 420], or for specific subtypes [245]. Some of the studies negating the prognostic significance of histologic typing may suffer from considerable drawbacks, such as tumor misclassification, low frequency of certain tumor types or clustering together of heterogeneous groups of lesions (as PapRCC subtypes).

Tumor stage is, as in many other human cancer, the best established prognostic factor [255, 372]. Tumor size thresholds used for grading were variously defined (Table 3). According to Zisman et al, the survival significantly worsens if the tumor diameter exceeds 4.5 cm, and using such thresholds maximizes the prognostic value of the classification [614].

According to Buchner et al, the detection of RCC cells in the bone marrow is not an independent prognostic factor, although some effect was observed in this study [64]. The series analyzed was, however, small and the data not corrected for other prognostic factors. Renal capsule infiltration and collecting duct invasion are not formally included into the current TNM system; however, these features may worsen the survival [265].

The first grading system was applied to RCC by Hand and Broders in 1932 [200]. Later, other systems were created (Table 4), but currently the one described by Fuhrman et al. has gained the widest acceptance [25, 163, 504, 539]. The Fuhrman grading system (Fig. 11) has a proven prognostic impact and is relatively easy to apply. Its shortcomings are non-fully standardized diagnostic criteria and limited reproducibility [143, 183]. The Kappa statistics value lies within the range of 0.2 to 0.45 [155, 296]. An improvement in agreement might be achieved by reduction of diagnostic groups to three or two, by combining the original Fuhrman categories. There is evidence that such a simplified scheme may retain the high prognostic value. In fact, in numerous series there is no difference in survival between grades I and II [296, 463]. In the material of Ficarra et al., indeed only this reduced system is useful for prognostication [155]. On the other hand, constructing a 3-tier classification induces the diagnostician to include the majority of cases into the intermediate category, lowering the discriminatory power of the classification. In a recent analysis it was suggested that the percentage of high grade (Fuhrman 3 and 4) areas may be an independent and highly effective determinant of survival [491].

Another question arises from the fact that the Fuhrman classification had been created before the current RCC classification was introduced and may not be equally useful for all the recognized tumor types. For example, chromophobe

TABLE 3
Staging of renal carcinoma

	TNM 1992 [509]	TNM 1997 [375]	TNM 2002 [17]
T1	Tumor below 2.5 cm in largest dimension, limited to the kidney	Tumor below 7cm in largest dimension, limited to the kidney	Tumor below 7cm in largest dimension, limited to the kidney
T1a			Tumor below 4cm in largest dimension, limited to the kidney
T1b			Tumor 4-7cm in largest dimension, limited to the kidney
T2	Tumor over 2.5cm in largest dimension, limited to the kidney	Tumor over 7cm in largest dimension, limited to the kidney	Tumor over 7cm in largest dimension, limited to the kidney
T3	Tumor infiltrates renal vein or adrenal or perirenal fat tissue, but without extending beyond Gerota's fascia	Tumor infiltrates renal vein or adrenal or perirenal fat tissue, but without extending beyond Gerota's fascia	Tumor infiltrates renal vein or adrenal or perenal fat tissue, but without extending beyond Gerota's fascia
T3a	Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia	Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia	Tumor infiltration into adrenal gland, perirenal fat or renal sinus fat, but not beyond Gerota's fascia
T3b	Tumor grossly extends into renal vein or its branches, or vena cava below diaphragm	Tumor grossly extends into renal vein(s) or vena cava below diaphragm	Tumor grossly extends into renal vein or its muscle containing branches, or vena cava below diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm	Tumor grossly extends into vena cava above diaphragm	Tumor grossly extends into vena cava above diaphragm or invades wall of vena cava
T4	The tumor infiltrating beyond Gerota's fascia	The tumor infiltrating beyond Gerota's fascia	The tumor infiltrating beyond Gerota's fascia
N1	Metastasis in a single lymph node, below 2cm in largest dimension	Metastasis in a single lymph node	Metastasis in a single lymph node
N2	Metastasis in a single lymph node, 2 to 5cm in largest dimension or multiple lymph node metastases, none larger than 5cm	Metastases in more than one lymph node	Metastases in 2 or more regional lymph nodes
N3	Metastasis or metastases over 5cm in largest dimension	-	-

(classes T0, Tx, N0, Nx, M were omitted)

TABLE 4
Selected renal cell carcinoma grading systems

	Skinner [504]	Syrjänen and Hjelt [524]	Fuhrman [163]
G1	nuclei identical to normal renal tubular epithelial cells	round homogeneous nuclei, finely dispersed chromatin, no visible nucleoli, mitotic figures rare	nuclear size ~10μm, regular outline, no visible nucleoli
G2	nuclei pycnotic and slightly irregular, with minimal enlargement and no abnormal nucleoli	nuclei are hyperchromatic, with irregular size and shape, nucleoli visible, mitoses rare	nuclear size ~15μm, outline slightly irregular, nucleoli visible by high magnification (40x lens)
G3	moderately enlarged, irregular and pleomorphic nuclei, with prominent nucleoli, but bizarre nuclei are absent	distinct irregularity of nuclei, prominent nucleoli, numerous mitotic figures	nuclear size ~20μm, clearly irregular, nucleoli visible by low magnification (10x lens)
G4	numerous bizarre and huge nuclei	-	bizarre, pleomorphic and multilobated nuclei
		concurrently: A well-delimited B poorly-delimited	

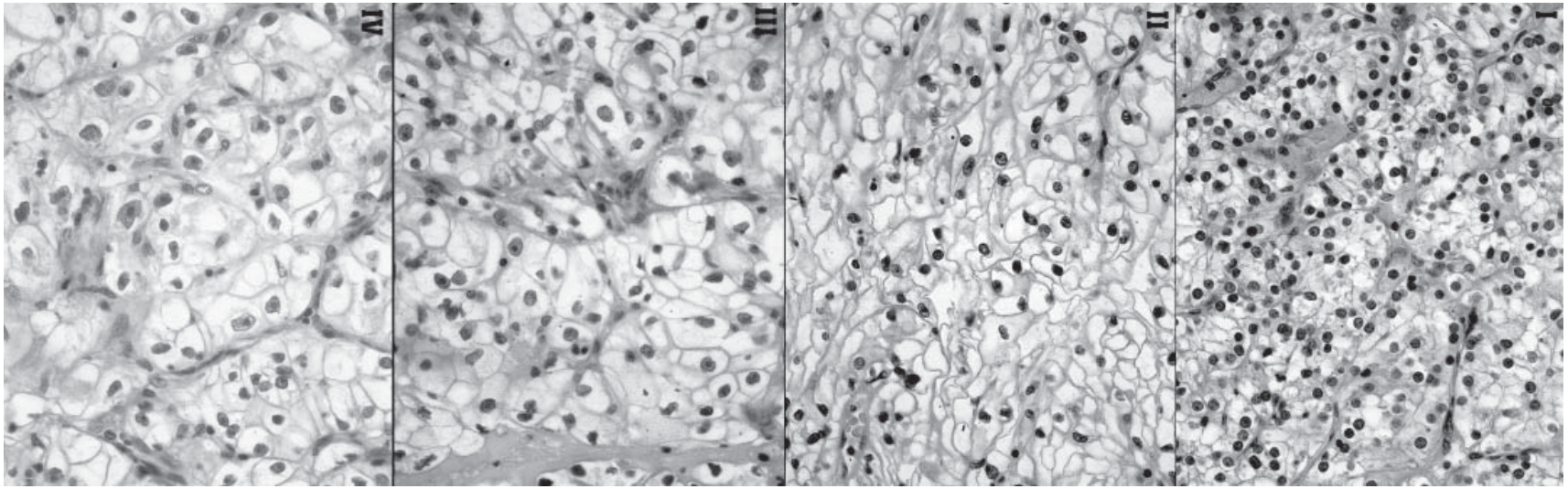

Fig 11. The Fuhrman grading of renal clear cell carcinoma. Hematoxylin-eosin, magnification 400x.

RCC often has irregular nuclei comparable with high grade CCRCC, but this seems not to alter the prognosis, especially if stage is taken into account [124, 332]. The Fuhrman grading system may be used for PapRCC; however, according to Sika-Paotonu et al, only nucleolar size gives prognostic information [499].

Several immunohistochemical markers or sets of markers were suggested as prognostic in RCC. The stain for CXCR3 is positive in a vast majority (96%) of RCCs, but the percentage of positive cells varies [268]. Tumors with less than 30% of positive cells behave significantly worse. This phenomenon may depend on the effect on neoangiogenesis or cellular immunity. MUC1 expression increases with cancer progression, is correlated with grade, stage and size of the tumor and may be an independent prognostic factor [311]. CD10 expression in CCRCC is seen in low-stage, low-grade tumors and thus it might be related to prognosis [298]. Reduced PTEN expression correlates with a shortened survival in RCC, but also with stage and grade and is not an independent prognostic factor [497]. According to Vasselli et al., VCAM-1 expression might be the most important biochemical prognostic factor in disseminated RCC. This observation is clearly associated with the role of this adhesion molecule in the immune response [565]. Another adhesion molecule, CD44, is known to participate in tumor progression and spreading in many cancers; in RCC its expression is an independent prognostic factor, although it is correlated with stage and grade [321]. Survivin is an antiapoptotic protein of prognostic significance in several cancers. In RCC, its expression was demonstrated in all major histologic types [343]. Kosari et al. identified survivin expression as one of the major factors identifying CCRCC with a poor prognosis [275]. Survivin expression was shown in 80% of RCCs. It was correlated with tumor size and grade; however, it was an independent prognostic factor [68, 283]. Cases with less than 2% of immunopositive cells show survival of around 87%, whereas survival in the remaining cases is around 43% [283, 416]. Complex models encompassing entire sets of markers may show a better performance than single markers. Kim et al. used a model that included Ki67, p53, gelsolin, CA9, CA12, PTEN, EpCam and vimentin [257]. A similar set employed by Shi et al. was analyzed by the "random forest" method [495]. The obtained clusters had prognostic significance and were in part compatible with the morphologic classification. The non-compatible cases showed significant morphologic differences from the bulk of typical cases.

In many cancers, necrosis is a poor prognostic sign; however, the data on the impact of necrosis on RCC prognosis are contradictory. In the material of Roosen et al, necrosis was an independent prognostic factor [471]. According to other authors, the presence and extent of necrosis are correlated with stage, size and grade of the tumors, as well as other prognostic factors, but in multivariate analysis necrosis is not and independent prognostic factor [292, 309]. In chromophobe carcinoma, Zini et al. found significant necrosis in tumors that did progress [612]; on the other hand, this analysis was based on a small sample (21 cases), of which in eight cases necrosis was present. This is a surprisingly high frequency; in our material, necrosis in chromophobe carcinomas was significantly less frequent (~10%). On the contrary, according to Kim et al, necrosis affects the prognosis in CCRCC, but not in chromophobe RCC [255]. Further studies are needed to clarify this issue.

Microvascular density (MVD) is known to affect tumor development and progression and in several cancers may be an independent prognostic sign. However, the results for RCC are contradictory. In some studies, microvascular density is proportionally related to survival, while in others, the relationship is inverse, as in the majority of non-renal cancers [250, 476]; in yet other studies, microvascular density has no prognostic significance at all [339]. Kirkali at al. found a significant relationship between vascular density in RCC and survival and rate of metastatic spread. Although vascular density in this study was not correlated with other prognostic factors, such as tumor stage and grade, in multivariate analysis only the TNM stage and proliferation index were independent prognostic factors [260]. Delahunt et al. found that 5-year survival rates in patients with MVD below and over 40/hpf were 39% and 64%, respectively. In this study, vascular density was, however, dependent on tumor stage and the prognostic significance limited to stage III tumors [121]. According to Baldewijns, high grade CCRCCs have a less developed vascular network, but endothelial cell proliferation, as well as VEGF expression, is more intense [39].

Another factor involved in survival is vascular invasion. Although renal vein invasion is included into the standard pTNM stage, invasion of smaller vessels is often neglected. Its frequency may be highly dependent on gross dissection method and is highly correlated with tumor relapse [106, 107].

As it has been discussed above, one of the important risk factors in RCC is overweight. There is evidence, however, that it may also affect survival. Surprisingly, in some studies, a better prognosis was observed in obese patients [598]. Kamat et al. stated that an increased BMI was even an independent prognostic factor [242]. Less definite results obtained by Donat et al. showed at least a non-inferior survival rate for overweight patients [131]. It was stated that tumors in overweight individuals were smaller, less advanced and lower grade. The survival rates in persons with BMI below 25 kg/m^2, in the range of 25 to 30kg/m^2 and

over 30kg/m^2 were, respectively, 62, 77 and 82%. In these studies, the multivariate models failed to show independent prognostic significance of overweight. The exact relationship between a high body mass and a lower stage of RCC remains unexplained, although it is thought that frequent medical check-ups and in consequence earlier detection of a tumor is not the dominant rationale [131, 417, 482].

Partial pan-European data (EUROCARE-3 program [97]) suggest a somewhat better 5-year survival rate in women (57.2 versus 54.2%). In Aron's material, tumors observed in females were smaller (the mean diameter of 5.9 versus 6.1cm) and were better differentiated. RCCs in males were more frequently locally advanced or disseminated. Consequently, the 5-year survivals were better in women than in men (69% versus 65%). However, in multivariate models, gender was not an independent prognostic factor [26]. Similar results were published by Onishi et al. and Woldrich et al. [402, 582]. It was surmised that these differences in renal cancers in males and females may depend on earlier detection by more frequent imaging studies in the latter, performed on request of their out-patient gynecologists. Renal cancer is, however, diagnosed at a later age in women than in men, what renders this explanation implausible [582]. Thus, a yet-unexplained, sex-related intrinsic aspect of RCC has to be involved. Aneuploidy is seen in 50% of CCRCC. Its presence is related to high grade and advanced stage, especially when the sarcomatoid component is present, and is a poor prognostic sign [329]. Due to the limited value of prognostic methods in RCC, there is an obvious temptation to use somewhat more sophisticated methods, such as quantitative pathology and image analysis. Stockle et al. successfully used such methods for renal tumors classification and obtained prognostic information [513]. Delahunt et al. identified several parameters of prognostic significance, beside the obvious tumor stage, such as nuclear surface area, diameter and elongation, nuclear organizers (AgNOR) count and PCNA expression [120]. Nativ et al. showed that nuclear quantitative parameters were of prognostic significance. The most relevant were ellipticity, surface area and form factor. If combined with tumor stage, distinction of localized and disseminated pT1-2 cases was possible [389]. In the study of Carducci and al., it was shown that the nuclear shape parameters provided prognostic information independently of stage and grade. Again, ellipticity was particularly important [71]. If ellipticity was combined with stage, three categories were identifiable, with overall relapse rates of 4, 37 and 63%. Quantitative parameters significantly improved classification prognostic performance over combined stage and grade. All these results show that although nuclear morphometry and the Fuhrman grade are applied to the analysis of the same tumor features, the former may be more effective, even though the papers cited employed relatively simple methods of image analysis.

Symptomatic and asymptomatic renal cancers do differ in their clinical prognosis. In the recent series, incidental cases constitute around 50% [108, 135, 435]. They are less advanced, with almost 60% below 4cm in diameter; the proportion of symptomatic tumors of this size is 20% only. In incidental cases, the 5-year survival rate exceeds 95%, compared with 60% in symptomatic cases [108, 135, 435]. Some renal tumors remain undetected until post-mortem examinations. In such material, symptomatic cases are of a significantly larger size (7.3 cm) as compared to incidental ones (2.6 cm) [253]. The presence of systemic symptoms is seen in high-stage tumors and by itself it bears a grim prognostic significance. It was even surmised that it may constitute the strongest indicator of prognosis in advanced RCC [245].

Zisman et al. created a system classifying RCC patients into three groups depending on stage, grade and Eastern Cooperative Oncology Group performance status [142, 615]. Such an approach seems to be a particularly robust method, with highly significant differences in survival between groups. Also the presence of coexistent diseases may strongly affect the survival. This factor is assessed formally by the Charlson index [27]. In the future, gene expression analysis may be expected to provide individual prognostic information. First attempts at such an approach were already published [565].

Remarks on Treatment

The performance of chemotherapy in RCC, both using single agents or their combination, is poor; the response rate may be as low as 6% [438, 586]. The high resistance of RCC to chemotherapy is not completely understood. In many cancers, multidrug resistance depends on the MDR1 gene product (P-glycoprotein H, MIM 158343 [234]); its role in RCC is controversial. P-glycoprotein level is high in RCC, parallelizing the relationships in normal renal tubular epithelial cells. According to some studies, P-glycoprotein is lower in higher grades [507, 549]. The transcription factor PAX2 is expressed in developing kidney cells and decreases their sensitivity to proapoptotic signals. Heuber et al. confirmed a similar effect in RCC cells, which are protected by PAX2 from cisplatin-induced apoptosis [223]. Oudard et al. analyzed several factors responsible for tumor resistance to chemotherapy. These included multidrug resistance protein, multidrug resistance-associated protein, glutathione-S-transferase-π, topoisomerase-IIα, thymidylate synthetase and thymidylate kinase. The thymidylate

kinase level was significantly higher in RCC as compared to a normal kidney, similarly as the levels of BAX and bcl-2. Expression of these proteins was largely independent of stage and grade of the tumor [407]. Another substance related to chemotherapy resistance is clusterin (MIM 185430 [234]). Clusterin is a glycoprotein involved in tissue remodeling, immune response, lipid transport and apoptosis regulation. In a non-neoplastic kidney, as well as in cancer, it was described to act as an antiapoptotic factor [138]. Miyake et al. found a high clusterin mRNA level in 50% of RCCs [371]. The cases with high clusterin expression showed a shorter overall survival and a shorter disease-free survival. Cancer cells transfected with the clusterin gene are increasingly resistant to cis-platinum [202] and antisence oligonucleotides repressing clusterin expression increase drug induced apoptosis [303, 610]. The effectiveness of radiotherapy in RCC is at best poor, although several authors affirm some reduction in local relapse rates [347]. However, no prolonged survival has been reported.

Until recently, the most frequently used adjuvant method for RCC was immunotherapy. The agents used are IL-2 and interferon α (INF). According to the studies that established immunotherapy as a standard, administration of high dose IL-2 may allow for a positive response in up to 20% of patients; however, the IL-2 responsiveness may be dependent of tumor COX-IX expression. The highest estimated response rate for INF is about 15%. Newest multicenter analyses are less optimistic in estimating immunotherapy effectiveness. In some reports, no therapeutic response was seen in patients with disseminated RCC, and only high dosage IL-2 may lead to a significant survival benefit [29, 391]. Preoperative immunostimulation using IL-2 may increase the survival after 1 year (81% versus 98%) and 5 years (73% versus 86%) [266]. Alternative immunotherapy methods may be developed. Activated T cells were proposed as a tool, including γδ cells [496]. Stem cells allografts were used with promising results in disseminated RCC patients [528]. Another adjuvant method is vascular embolization. This may be used either as a preoperative measure or in palliative care [56, 573, 611]. In selected cases, such as multiple angiomyolipomas in tuberous sclerosis, it is the treatment of choice.

Targeted Therapy

The change we are currently experiencing in RCC treatment is the introduction of targeted drugs, tailored to specifically affect the signaling pathways involved in cancer development and progression [51, 172, 324, 379]. The agents recently approved by the American and European drug agencies are Sunitinib, a tyrosine kinase VEGFR-2 and PDGFR-β inhibitor [367, 379, 380, 381], Sorafenib, a tyrosine kinase inhibitor, acting on multiple cellular receptors, including VEGFR [59, 146] and bevacizumab, a monoclonal antibody directed against VEGF [146]. The estimated cost of treatment is in the range 5,000 to 10,000$. It is one of the reasons for a careful patient selection. The other is the appearance of significant side effects [379]. The development of these drugs is a reason for a more cautious differential diagnosis in the case of RCC. In fact, the agents interacting with the VEGF signaling pathway were developed for CCRCC. On the other hand, Choueiri et al. analyzed their use for PapRCC and ChRCC and they found some beneficial effect, although less evident than in CCRCC [84]. Another interesting effect of Sunitinib and Sorafenib is the reappearance of endothelial adhesion molecules; this might enhance sensitivity to immunostimulants [29, 367, 572]. The combined antiangiogenic approach may be more effective than single agent therapy; this assumption was not, however, tested in vivo so far [40]. Some evidence exist indicates Sunitinib and Sorafenib may be effective even in patients resistant to other forms of treatment [533]. Axitinib, with the activity profile similar to Sorafenib, may cause tumor regression in as many as 44% of patients with disseminated RCC resistant to immunostimulation [324, 465, 465].

Beside the above listed agents, other drugs and potential drug targets are analyzed or currently undergoing clinical trials. Thalidomide, the infamous tranquilizer and teratogen, was recently introduced to cancer treatment. One of the mechanisms of action would be the interaction with angiogenesis. Some evidence points against its effectiveness in RCC, as no specific effect was shown in a mouse model and expression of VEGF remained unaltered [133]. A more interesting candidate might be rapamycin derivates, including Temsirolimus. It was shown that a survival benefit may be obtained by its administration, alone or in combination with INF. The mTOR pathway is an obvious target for tumors depending on its activation, like in tuberous sclerosis patients [221, 222]. The toll-like receptors (TLR), the components of innate immunity system, are also potential targets of treatment. TLR3 expression was shown to be increased in RCC and its inhibition results in specific growth impairment of the tumor cells [376, 483]. Survivin expression was demonstrated in all major RCC types [343] and it was proposed as a potential treatment target. However, its high expression in normal tubular epithelial cells may exclude its practical use [302]. EGF-R overexpression is described in 70% of RCC cases. ZD1839, an EGF-R inhibitor, reduces RCC cells proliferation rate, as well as VEGF and IL-8 production [28]. Obviously, elements common to many pathways would be of great interest as drug targets. One of these might be mitogen activated protein kinases

(MAPK), transferring signals for cell cycle, apoptosis inhibition and angiogenesis. Inhibition of proliferation, reduction of angiogenesis and necrosis were seen as the result of effects exerted on MAPK in RCC [220].

Treatment of tumor types other that CCRCC may require other strategies. Imatinib, which interacts with the c-KIT receptor, was considered for use in ChRCCs, which overexpress KIT. However, the c-KIT gene mutations, required for Imatinib to act, were not confirmed in this tumor; moreover, this low grade cancer is curable by surgery only in most cases [197, 428]. More interestingly, Castillo et al. showed that tumors with the sarcomatoid component frequently express KIT and might be affected by Imatinib [74]. Still, the c-KIT gene mutations are rare (~5%), making a response to the drug unlikely in the majority of cases [490]. A subset of PapRCC, especially advanced stage type 2 tumors, might require chemical treatment. The obvious target is the HGF/c-MET signaling pathway. Anti-HGF antibodies, anti-MET antibodies and small-molecule MET receptor inhibitors are tested [43, 67, 88, 165, 377]. Although the mutated protein may be less sensitive to inhibition, some in vitro research attempts are promising. Clinical trial results are, however, not available at the moment and the trials themselves may require more time to complete, because of the relative rarity of advanced stage, high grade PapRCC.

Surgery

Although following the introduction of radical nephrectomy, surgical methods did not change significantly for a long time, in the last years, a substantial progress has been seen. Particular attention is paid to nephron-sparing and "patient-sparing" methods. These include in the first place endoscopy and partial nephrectomy. Radical endoscopic nephrectomy is becoming a standard method for T1/T2 tumors. The achieved oncological results are at least not worse than those obtained by using the traditional approach. Some studies even suggest that patients' survival may improve due to lower cardiovascular complication rate [206, 543].

Another surgical method that is becoming standard is partial renal resection for tumors below 4 cm in diameter. In this group of patients, the results seem to be excellent. MacKiernan et al. analyzed a series of 292 renal tumors; for CCRCC, the 5-year survival rate was over 90%, with the rate of relapse amounting to 12% [364].

Partial nephrectomy is usually limited to tumors of 4 cm and less in size. Some authors suggest that this may not be an absolute requirement [308, 409, 421]. Pahernik et al. obtained the results comparable to radical nephrectomy in more advanced tumors. A more appropriate partial nephrectomy inclusion criterion would be the possibility of total tumor removal and not merely tumor size. In fact, stage III tumors showed higher mortality if treated by nephron-sparing methods. An issue of vivid interest for the pathologist, yet still controversial, is morcellation versus removal of the entire organ during laparoscopic nephrectomy. Removing an intact kidney requires a longer incision, which, according to some authors, largely thwarts the benefits of laparoscopy. On the other hand, morcellation significantly decreases the body of information obtained by pathological examination of the specimen. In particular, the extrarenal extension becomes unrecognizable and may lead to tumor understaging, even in small lesions [186]. In fact, histological assessment determines a significantly higher stage of the tumor in comparison to preoperative imaging in 20% of cases. Even 30% of small renal tumors resected by laparoscopy may require additional treatment or examinations, which would be neglected without histologic results [94].

An approach combining partial resection with laparoscopy was attempted; however, it is still non-standard and used only in some centers [519]. In recent series, an increasing proportion of tumors are small, rendering the use of less radical surgical methods more desirable [99]. On the other hand, in case of some advanced tumors, nephrectomy may be followed by tumor resection with autotransplantation of the remaining parts of the kidney. This may increase the risk of cancer progression and may be of benefit in selected patients only. A careful follow-up would be essential in these cases [141].

Radiofrequency ablation may be a safe alternative for treating small tumors. It may be also used in large, inoperable lesions or in patients in a poor general condition. The principal disadvantage is lack of proper control of the effect on the tumor and the histological diagnosis being limited to the biopsy material [62, 559, 577]. The watch and wait approach in selected small RCC cases was attempted, but this is associated with a significant oncologic risk and may be an option only in patients in whom neither total nor partial nephrectomy is feasible [563].

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