The International Society of Urological Pathology (ISUP) Grading System for Renal Cell Carcinoma and Other Prognostic Parameters

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Abstract: The International Society of Urological Pathology 2012 Consensus Conference made recommendations regarding classification, prognostic factors, staging, and immunohistochemical and molecular assessment of adult renal tumors. Issues relating to prognostic factors were coordinated by a workgroup who identified tumor morphotype, sarcomatoid/rhabdoid differentiation, tumor necrosis, grading, and microvascular invasion as potential prognostic parameters. There was consensus that the main morphotypes of renal cell carcinoma (RCC) were of prognostic significance, that subtyping of papillary RCC (types 1 and 2) provided additional prognostic information, and that clear cell tubulopapillary RCC was associated with a more favorable outcome. For tumors showing sarcomatoid or rhabdoid differentiation, there was consensus that a minimum proportion of tumor was not required for diagnostic purposes. It was also agreed upon that the underlying subtype of carcinoma should be reported. For sarcomatoid carcinoma, it was further agreed upon that if the underlying carcinoma subtype was absent the tumor should be classified as a grade 4 unclassified carcinoma with a sarcomatoid component. Tumor necrosis was considered to have prognostic significance, with assessment based on macroscopic and microscopic examination of the tumor. It was recommended that for clear cell RCC the amount of necrosis should be quantified. There was consensus that nucleolar prominence defined grades 1 to 3 of clear cell and papillary RCCs, whereas extreme nuclear pleomorphism or sarcomatoid and/or rhabdoid differentiation defined grade 4 tumors. It was agreed upon that chromophobe RCC should not be graded. There was consensus that microvascular invasion should not be included as a staging criterion for RCC.

Key Words: pathology, kidney, renal cell carcinoma, tumor morphotype, grade, necrosis, sarcomatoid differentiation, rhabdoid differentiation, microvascular invasion, International Society of Urological Pathology

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Outcome prediction for renal cell carcinoma (RCC) has been the subject of detailed study, and to date >3600 separate reports relating to this have been published since 1946 (Ovid MEDLINE, Keywords: renal cell carcinoma and prognosis, accessed August 8, 2012). Despite this intense activity, prognostic assessment of RCC remains controversial, and few parameters have been validated and are reported on in routine clinical practice.

The clinical and scientific relevance of prognostic factors for RCC were considered by a work group of the Rochester RCC Conference convened at the Mayo Clinic, Rochester, MN in March 1997.[1] This group classified prognostic parameters according to the College of American Pathologists Working Classification for Prognostic Markers and concluded that tumor morphotype, tumor grade, and sarcomatoid architecture were the only histologic parameters that were well supported in the literature and regularly used to inform patient management. These conclusions themselves were, however, limited, with clear cell RCC morphotype being considered to be the unfavorable prognostic feature for tumor morphotype; grading was assessed on the basis of low-grade and high-grade morphology, although no individual tumor grading system was specified.

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Despite this limited consensus, there remains debate as to the validity of these apparently established parameters. In particular, there are contradictory results relating to the predictive value of tumor morphotype,[2] whereas recent reports have questioned the validity of Fuhrman grading for the 3 main morphotypes of RCC.[3–6] In view of this, it was determined that a detailed assessment of prognostic factors would be subjected to consensus agreement to identify parameters having clinical application and to provide for reporting uniformity.

INTERNATIONAL SOCIETY OF UROLOGICAL PATHOLOGY CONSENSUS CONFERENCE

To identify the current opinion regarding the classification, prognostic factors, staging, and molecular biology of adult renal tumors, a web-based questionnaire was distributed to all members of the International Society of Urological Pathology (ISUP). Those members who completed this electronic survey, as well as working group members responsible for the preparation of the survey, were invited to participate in a consensus conference convened in association with the 2012 Annual Scientific Meeting at the United States and Canadian Academy of Pathology. The aims of this conference were to make recommendations relating to the formulation of a contemporary classification of adult renal tumors and the identification of clinically significant prognostic factors, improved staging criteria for major RCC morphotypes, and molecular and immunohistochemical markers of diagnostic and prognostic significance. The detailed processes relating to the survey and consensus meeting are reported elsewhere.[7]

At the conference, representatives from the 4 workgroups appointed to coordinate the consensus process presented background information and the results of detailed literature reviews to the meeting. After discussion, a series of questions relating to relevant controversial issues were put to electronic ballot, and in accordance with established practice, an achievement of 65% agreement on voting was considered to be a consensus.[8]

The results of each of the working group reports relating to the classification of adult renal tumors, tumor staging, and molecular and immunohistochemical diagnostic and prognostic markers are reported separately.[9–11]

As part of the preparation for the consensus conference, members of the Prognostic Factors Workgroup (work group 2) were asked to identify those prognostic parameters they considered to be of clinical relevance for RCC. The results were collated and circulated to all work group members, and an agreement was reached on which parameters should be further evaluated. Of the various parameters considered, tumor morphotype, sarcomatoid morphology, rhabdoid morphology, tumor necrosis, tumor grade, and microvascular invasion were identified as being worthy of consideration by the full consensus conference.

TUMOR MORPHOTYPE

In the past 30 years considerable research activity has shown RCC to represent an heterogenous group of tumors rather than a single entity, as had been considered historically. This is well reflected in a comparison of the 1981 World Health Organization (WHO) classification, with the most recent classification published in 2004.[12,13] In 1981 renal epithelial malignancy was classified as *RCC* or *Other*, whereas in the 2004 classification 9 distinct morphotypes were recognized. More recently, further novel forms of RCC have been described, and a contemporary classification is presented by working group 1.[9] Recent studies have confirmed that many of these various morphotypes of RCC show differences in genotype and gene expression[4,14–20]; however, whether these genetic differences are more predictive of outcome than traditional parameters, such as stage, grade, and performance status, remains open to debate.

The consensus conferences held in Heidelberg (1996) and Rochester (1997) laid the foundations for the modern classification of RCC through a formal definition of the most commonly encountered forms of RCC—clear cell, papillary and chromophobe RCC, and collecting duct carcinoma—which themselves account for 85% to 90% of renal tubular malignancies.[21,22] The remaining 10% to 15% of tumors routinely encountered in clinical practice include a variety of uncommon carcinomas and a number of tumors that have yet to be formally classified.

Until 1997, few studies had evaluated the prognostic impact of RCC morphotype, and much of the published data are hampered by a failure to recognize the prognostic significance of many of the additional morphotypes that have been subsequently described. More recent studies, which have been institutional and are based on pathologic slide review, have shown papillary and chromophobe RCC to present at lower pathologic stage, to have lower nuclear grades, and to have a lesser risk for metastasizing after treatment, when compared with clear cell RCC. Furthermore, it has been shown that patients with clear cell RCC have a significantly lower cancer-specific survival rate when compared with those with either papillary or chromophobe RCC, whereas the outcomes of patients with papillary or chromophobe RCC of comparable stage are similar.[4,14–17]

Surprisingly, these findings were not confirmed in the largest multi-institutional study reported to date, which consisted of 4063 patients. The study, however, differed from those reported earlier, as no formal diagnostic slide review was undertaken. There were further limitations relating to a relatively small sample size for certain stage-specific histologic categories and a failure to include collecting duct RCC in the analysis.[18] There also seemed to be a geographic bias relating to the country of origin, with increased numbers of high-stage cancers being reported from North American sites.

Recently, a National Cancer Institute Surveillance Epidemiology and End Results Program (SEER) study noted, in both univariate and multivariate models, that morphologic subtyping of RCC was an independent

predictor of cause-specific mortality. Despite this, the variable added little to the overall accuracy of a prognostic model that included TNM categories, tumor grade, and patient age. Although this finding is important in establishing the role of RCC subtyping in cause-specific mortality, the study was limited by the inclusion of data collected before the publication of the Heidelberg/Rochester Consensus Classification, which meant that there was likelihood that a number of tumors would have been misclassified. In particular, there was a failure to recognize collecting duct RCC as a distinctive tumor entity.[19]

In a recent large multi-institutional study of 5339 patients from Italy, these issues were addressed through the inclusion of collecting duct RCC as a distinct morphotype in the analysis. In this study, histologic subtype was shown to be a predictive variable for cancer-specific mortality in univariate analysis and in multivariate analysis that included sex, symptom status, pT, N, and M staging category, and tumor grade.[20]

Most recently, reports from a single-center analysis of 3062 patients treated surgically for unilateral, sporadic RCC have shown clear versus nonclear histology to be a predictor of cancer-specific and metastasis-free survival, on multivariate analysis, even after controlling for stage, grade, and other prognostic variables.[23] The importance of central pathologic slide review is highlighted by the findings of this study, as 20% of the carcinomas originally classified as papillary RCC were reclassified as clear cell RCC. The significance of this is reinforced by the observation that 5-year cancer-specific survival probabilities of patients with papillary RCC ranged from 80% to 90% in studies in which slide review was undertaken, whereas these probabilities were as low as 70% in a study in which this was not performed.[4,17]

In 1997, Delahunt and Eble[24] divided papillary RCC into 2 subtypes (types 1 and 2) on the basis of morphologic criteria, and the validity of this has been confirmed by genetic profiling. Multiple studies have evaluated the prognostic significance of this subtyping, demonstrating that type 2 papillary RCCs are usually of higher stage and grade when compared with type 1 tumors.[25–27] Despite this, issues relating to the prognostic value of subtyping remain, and to date there is debate as to the prognostic relevance of this subclassification. Many of the available studies have confirmed that type 2 papillary RCC has a worse outcome in multivariate analysis,[26,28] although in other studies no association was demonstrated for disease recurrence and cancer-specific survival. It is clear, however, that as different percentages of type 1 and type 2 tumors are reported in the large series,[24–26,29,30] there are issues relating to classification of tumors. It is apparent that the correct identification of the papillary RCC subtype often requires experience, as many tumors may display prominent papillary (or pseudopapillary) architecture, such as collecting duct carcinoma, MiTF-TFE/TFE family translocation–associated renal carcinomas, hereditary leiomyomatosis–associated RCC, and acquired cystic disease–associated RCC,[31] and are subject to misclassification as type 2 papillary RCC.

Of the less common morphotypes of RCC, the poor prognosis of collecting duct RCC is well documented. These are high-grade carcinomas with an infiltrative growth pattern. When small they are predominantly located in the renal medulla, whereas larger neoplasms frequently involve the cortex. One third to one half of cases have metastases at presentation, with the most common metastatic sites being the lymph nodes (44%) and abdominal and thoracic viscera (32%), with lung (17%) being the most common. More than 50% patients present with flank pain, mass, and hematuria. Five-year cancer-specific survival ranges from 45.3% to 58%.[32,33]

Prognostic assessment of recently described morphotypes of RCC such as the MiTF-TFE family translocation–associated RCC, acquired cystic disease–associated RCC, tubulocystic RCC, and clear cell tubulopapillary RCC is hampered by the small number of cases reported in the literature, with extended clinical follow-up information too limited to permit any meaningful conclusion.[34] Despite this, evidence to date suggests that most clear cell tubulopapillary RCCs are small and confined to the renal parenchyma at presentation and subsequently exhibit an apparently indolent clinical course.[35]

Consensus Decisions

At the Consensus Conference, there was strong consensus (98%) that the main morphotypes of RCC have prognostic significance. There was also consensus (73%) that for papillary RCC, differentiation between type 1 and type 2 tumors has prognostic significance. For clear cell tubulopapillary RCC, there was agreement (85%) that this morphotype was associated with a more favorable outcome than papillary RCC or clear cell RCC. On the basis of the understanding that too few cases had been subjected to outcome studies, there was no consensus as to whether or not tubulocystic RCC was associated with either a poor or more favorable outcome, when compared with clear cell RCC. There was similarly no agreement as to whether or not a specific genotype was of prognostic significance for tumors of the MITF/TFE translocation RCC tumor group (MIT family).

SARCOMATOID DIFFERENTIATION

RCC with sarcomatoid features[4,13,36–62] is not currently recognized as a specific type of renal parenchymal carcinoma by the WHO[13] or by other classifications of renal neoplasia published subsequent to the Heidelberg renal tumor consensus meeting of 1996.[21] This is mainly because of the observation that sarcomatoid areas can be found in all histologic subtypes of RCC. Despite this, reporting of sarcomatoid change is recommended,[54,61] as this is an indicator of a poor prognosis, with potential treatment implications.[53,55,59]

Sarcomatoid RCC, on the basis of a survey of the 5 largest published series, with over 100 patients in each, affects patients of a mean age of 56 to 61 years (range, 33 to 87 y).[41,45,52,60] Approximately 90% of patients are symptomatic at presentation, due either to the effects of

the primary tumor or metastasis.[41,52] Pain and hematuria are common symptoms, whereas weight loss, fatigue, and gastrointestinal and respiratory symptoms are reported by a minority of patients.[52] Patients typically present with advanced-stage disease and distant metastases are present in 45% to 77% of patients at the time of primary treatment.[41,45,52,60] Multiple sites of metastasis are detected in 42% of cases, with lungs and bones being the most common sites of secondary spread.[52]

Preoperative identification of sarcomatoid RCC is limited, as radiologic findings are not specific and needle biopsy has a very low sensitivity in detecting the sarcomatoid component within an RCC.[36,59] Grossly, tumors with sarcomatoid RCC are large, being 9 to 11 cm in mean diameter (range, 3 to 25 cm).[41,45,52,60] The cut surface is often described as soft, fleshy, and gray-white, with infiltrative margins. Microscopically, the neoplasms are usually biphasic, with both carcinomatous and sarcomatoid components, and in typical series, sarcomatoid elements are seen in 1% to 8% of RCCs. In most cases, the associated RCC is of clear cell type, but a sarcomatoid element may also be seen in chromophobe, papillary, collecting duct, mucinous tubular and spindle cell, acquired cystic disease–associated, and unclassified carcinomas.[4,13–15,37,41,42,45,50,52,57,58,60] The sarcomatoid element is most often fibrosarcoma like with intersecting fascicles of malignant spindle cells (Fig. 1), pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma like), or of an unclassified morphology.[45,58] Heterologous differentiation along the lines of chondrosarcoma, osteosarcoma, or rhabdomyosarcoma is rare.[45,51,57] The sarcomatoid and carcinomatous areas may be intermingled or may show a sharp demarcation (Fig. 2).

The diagnosis of biphasic sarcomatoid RCC does not require use of special studies such as electron microscopy, immunohistochemistry, or molecular genetics. Genetically, sarcomatoid RCC is characterized by a complex set of chromosomal gains and losses, with losses common on 13q (75%) and 4q (50%).[39,48] Although

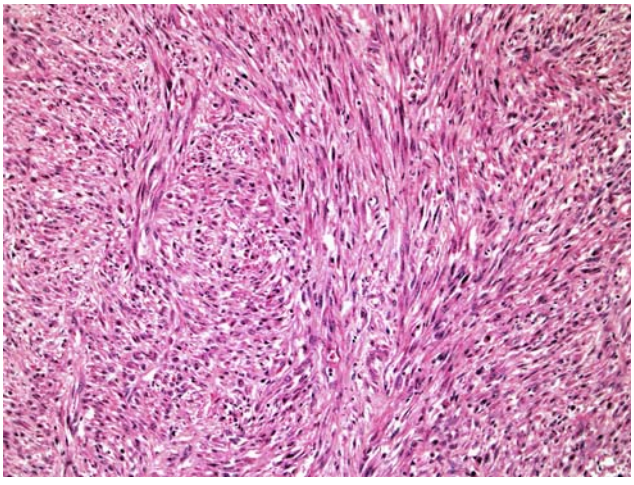

FIGURE 1. Sarcomatoid carcinoma with fascicles of malignant spindle cells.

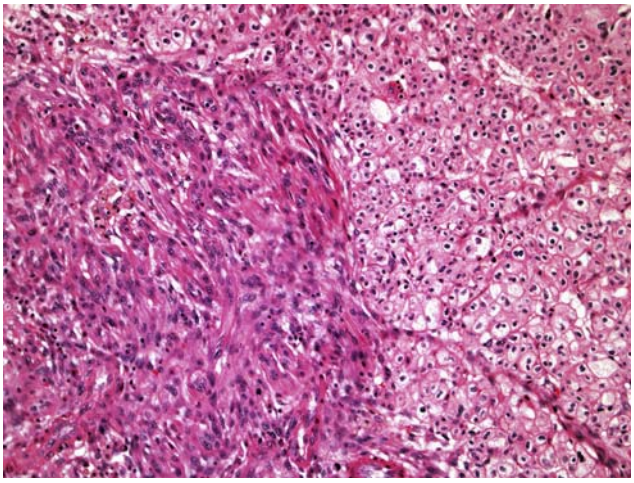

FIGURE 2. Sarcomatoid component within a chromophobe RCC.

X-chromosome inactivation data indicate that clear cell RCC and sarcomatoid carcinoma arise from the same progenitor cell, there are genetic differences between the 2 components, suggesting genetic divergence during clonal evolution.[49]

Sarcomatoid RCC has a dismal prognosis, with a median survival of 4 to 9 months after diagnosis[59] and a 15% to 22% five-year cancer-specific survival at 5 years.[41,45] As some patients survive 5 years, studies have been carried out to assess for prognostic indicators for sarcomatoid RCC, and multivariate analyses have demonstrated that TNM stage, performance status, tumor size, and metastasis are of prognostic significance.[45,60]

Consensus Decisions

The 6 questions relating to sarcomatoid RCC posed in the survey focused on the histomorphologic definition of sarcomatoid RCC, on whether a minimum amount of sarcomatoid tumor was needed for the diagnosis and quantitation of the area of sarcomatoid differentiation, on the reporting of the underlying subtype, and on the classification of tumors with a pure sarcomatoid morphology (Table 1).

Sarcomatoid RCC was originally defined by Farrow as "a carcinoma, intimately associated with a more pleomorphic spindle cell or giant cell malignancy resembling sarcoma."[47] An RCC has often been considered to harbor sarcomatoid foci when high-grade malignant spindle cells are present.[41,45,54] At the consensus conference the question of the definition of sarcomatoid RCC was addressed; however, there was no consensus. The largest percentage (41%) of participants felt that a tumor is sarcomatoid if it consists of atypical spindle cells and resembles any form of sarcoma. A significant percentage of participants (34%) voted that a spindle cell morphology need not be present as long as the tumor is very atypical and resembles any form of sarcoma. Another group (22%) considered a tumor sarcomatoid if it had a spindle cell pattern. Very few (3%) of the respondents

TABLE 1. Results of Survey Questions and Consensus Conference Voting Relating to Sarcomatoid and Rhabdoid Differentiation

	Survey Results		Consensus Conference Results		
Question	**%**	**Total**	**%**	**Total**	**Consensus**
Sarcomatoid differentiation					
Diagnostic features					
Epithelial cell elongation	4	206	3	117	Variable practice, no consensus
Spindle cells	34		22		
Atypical spindle cells resembling sarcoma	31		41		
Atypical sarcoma cells even without spindle cell morphology	31		34		
Reporting of underlying tumor type?					
Yes	90	205	94	120	Consensus
No	10		6		
Minimum % required?					
Yes	22	204	29	118	Consensus
No	78		71		
Sarcomatoid area (%) reported?					
Yes	77	204	NA		
No	23				
How area reported?					
%	68	158	NA		
Focal or extensive	36				
Other	1				
Reporting tumor with sarcomatoid morphology only					
1. Unclassified	10	203*	1	111	Consensus
2. Unclassified with sarcomatoid component	85		21		
3. Grade 4	42		10		
4. Categories 2 + 3	—		77		
Rhabdoid differentiation					
Report if present					
Yes	—	NA	74	121	Consensus
No	—		26		
Report underlying subtype?					
Yes	84	202	99	115	Consensus
No	16		1		
Rhabdoid area % reported?					
Yes	61	200	21	117	Consensus
No	39		79		
How area reported?					
%	65	131	—	NA	
Focal or extensive	34		—		
Other	1		—		
Reporting of tumor with rhabdoid morphology only					
Unclassified carcinoma	10	202*	—	NA	
Unclassified carcinoma with rhabdoid component	85		—		
Grade 4	37		—		

*More than 1 response permitted.
NA indicates not asked.

considered a tumor to be sarcomatoid if it showed early sarcomatoid change characterized by elongation of epithelial tumor cells.

The amount of sarcomatoid change in RCC has been reported in the literature to vary from 1% to 100%, but very few studies have specified the amount of sarcomatoid tumor needed to diagnose sarcomatoid change. One investigation required that a distinct spindle cell component of at least 1 microscopic low-power field ($\times 40$) be present to categorize the RCC as sarcomatoid.[45] The percentage of sarcomatoid change was a significant prognostic indicator in univariate analysis in 3 of 4 series of >100 patients, but it was not significant in multivariate analysis.[41,45,52,60] However, in 1 retrospective investigation on bevacizumab therapy, patients with a lower percentage of sarcomatoid component ($< 20\%$) had a better outcome.[59] There was a consensus among participants (71%) that a minimum proportion of sarcomatoid tumor was not required to make a diagnosis of sarcomatoid carcinoma, and on this basis there was informal agreement that it was not necessary to report the area of sarcomatoid tumor present.

Sarcomatoid RCC may arise out of a background of any histologic type of RCC as a manifestation of a final common dedifferentiation pathway.[43] Collecting duct carcinoma exhibits the highest percentage of cases with

sarcomatoid alteration ranging from 25% to 29% in separate series.[45,58] Clear cell RCC displays sarcomatoid change in 5.2% to 8% of cases, compared with 2% to 9% by chromophobe RCC, and 1.9% to 5.4% by papillary RCC.[15,41,45,56] The histologic type of the carcinomatous component does not appear to impact upon prognosis.[41,45] Despite this, metastatic deposits of sarcomatoid RCC may harbor only the carcinomatous component,[58] such that knowledge of the histologic type of carcinoma in the primary tumor would be useful in this setting. In addition, there may be a better, albeit modest, response to tyrosine kinase inhibitor or bevacizumab therapy for sarcomatoid RCC with a clear cell RCC component when compared with a non–clear cell RCC component,[53,59] although these findings should be validated in large, prospective, randomized clinical trials. There was a consensus (94%) that the underlying subtype should be reported for sarcomatoid RCC.

The final consensus meeting question addressed grade and typing of RCC with sarcomatoid morphology only. A pure sarcomatoid pattern is uncommon, being reported in 4% of all sarcomatoid carcinomas in 1 series.[4] According to the WHO classification, pure sarcomatoid tumors should be categorized as unclassified RCC,[13] and sarcomatoid RCC has been considered as Fuhrman grade 4.[41] A consensus (85%) was achieved in the conference that these pure sarcomatoid tumors should be diagnosed as grade 4 unclassified carcinomas with a sarcomatoid component.

RHABDOID DIFFERENTIATION

Rhabdoid differentiation in RCC refers to the development of neoplastic cells that morphologically resemble rhabdomyoblasts but differ in ultrastructural features and immunophenotype. This form of differentiation has been generally associated with a poor prognosis and is often present in tumors with a poorly differentiated morphology.[63–65] The current WHO classification of RCC does not include the rhabdoid phenotype as a distinct histologic entity, and as with sarcomatoid differentiation, the development of a rhabdoid morphology appears to represent a common dedifferentiation pathway for renal parenchymal malignancies, with clonal progression to a high-grade aggressive biological state.

Tumors showing rhabdoid differentiation are more likely to present at a higher stage with frequent extrarenal extension, having an aggressive biological behavior similar to that of sarcomatoid RCC.[66] Rhabdoid differentiation, also known as "composite" tumor,[67] is most frequently associated with clear cell RCC,[68] and in various series the rhabdoid component represented 5% to 90% of the tumor. Although rhabdoid differentiation is usually found in association with clear cell RCC, tumors showing this morphology have also been observed in papillary and chromophobe RCC (Fig. 3), collecting duct carcinoma, malignant mixed epithelial and stromal tumor of the kidney, acquired cystic disease–associated RCC, and medullary carcinoma.[50,63,66,67,69–71]

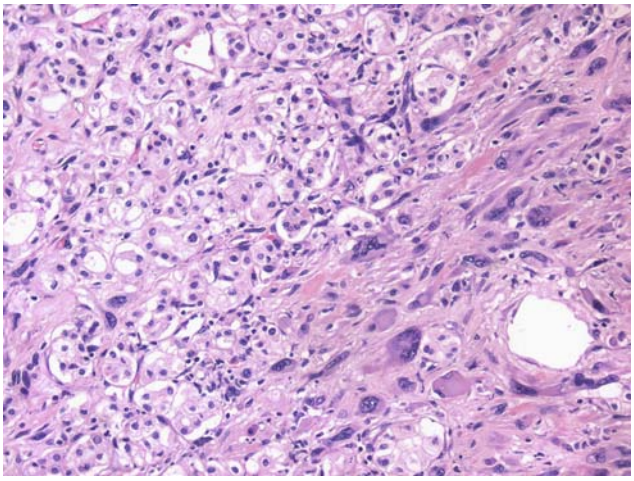

FIGURE 3. Rhabdoid morphology (right) in association with chromophobe RCC.

In adult RCC, rhabdoid differentiation is characterized by the presence of variably cohesive large epithelioid cells with central eosinophilic intracytoplasmic inclusions,[63] with large, eccentric, and irregular nuclei and prominent nucleoli (Fig. 4). Architecturally, most of the rhabdoid areas showed a solid growth pattern (Fig. 5), consisting of an organoid (78%) and/or a sheet-like (30%) arrangement of the tumor cells. Variant configurations such as pseudoglandular (9%) (Fig. 6), lymphomatoid (9%), and spindle cell (5%) patterns are encountered less commonly, with patterns admixed in 30% of cases.

Ultrastructurally, the paranuclear intracytoplasmic hyaline globules or inclusions contain whorled aggregates of intermediate filaments and/or coalesced degraded

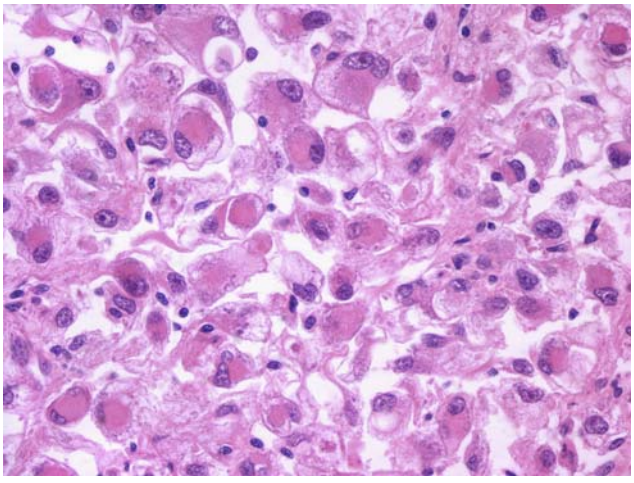

FIGURE 4. Rhabdoid cells are variably cohesive large epithelioid cells with central eosinophilic intracytoplasmic inclusions. Nuclei are large, irregular, and eccentric with prominent nucleoli.

organelles.[63,66] Some of the rhabdoid RCC studied by Godken et al[63] showed that the ultrastructural basis for the cytoplasmic globular inclusions seemed to be related to condensation of cytoplasmic organelles, rather than filamentous inclusions. This finding suggests that rhabdoid inclusions at a histologic level are heterogenous and highlights the continuing importance of electron microscopy in the characterization of rhabdoid cells.

Areas of rhabdoid morphology do not represent metaplastic muscle differentiation. Rhabdoid tumor cells mimic rhabdomyoblasts of rhabdomyosarcoma or tumor cells of pediatric renal rhabdoid tumors and should be differentiated from eosinophilic cells frequently seen in usual RCC. Rhabdoid RCC differs from pediatric rhabdoid tumors in that it lacks biallelic inactivation of the *hSNF5/INI1* gene. INI1 protein expression is positive in the rhabdoid cells of RCC, except for those associated with renal medullary carcinoma.[65,72]

The similar immunophenotype of rhabdoid and nonrhabdoid foci (cytokeratin$^+$, EMA$^+$, vimentin$^+$) supports the origin of the rhabdoid cells from classifiable-type RCC.[68,73,74] The epithelial origin of the rhabdoid cells, coupled with the common observance of transition areas between RCC and rhabdoid morphology, has led to the speculation that rhabdoid cells do not arise de novo but, instead, likely represent clonal and morphologic evolution of neoplastic RCC epithelial cells.[63] Further evidence for this conclusion has been shown by the presence of identical mutations in the rhabdoid and clear cell areas in 3 of 5 cases of RCC with rhabdoid features.[67,68,70] These observations suggest that the clear and the rhabdoid cells originate from the same clone and exhibit divergent differentiation. This supports the presumption that rhabdoid cells represent a dedifferentiation of RCC similar to sarcomatoid RCC. It is noteworthy that rhabdoid foci are occasionally seen in RCC with sarcomatoid change (Fig. 7).

There are approximately 75 reported cases of adult RCC with rhabdoid morphology.[63,66–68,70,73–75] These few cases have demonstrated a male predominance (M:F = 2:1), presenting from the third to eighth decade, with the mean age ranging from 52 to 63 years. In 4 retrospective series, encompassing a total of 1131 patients, the incidence of rhabdoid features ranged from 3% to 7% of RCC cases.[76] Studies have shown that RCC with a rhabdoid component have an aggressive clinical behavior and poor prognosis and are twice as likely to show extrarenal extension and distant metastasis compared with RCC lacking rhabdoid areas. Metastases occur in up to 70% of cases, and the cancer-specific mortality rate is 40% to 50%.[63,67,68] Sites of distant metastases reported to date include lung, bone, liver, adrenal gland, and diaphragm.[67,74] The few case reports and small series available describe median survival rates ranging from 8 to 31 months.[66,68,69,74,77] Patients in the largest series were treated with radical nephrectomy,[63,68] although 2 recent

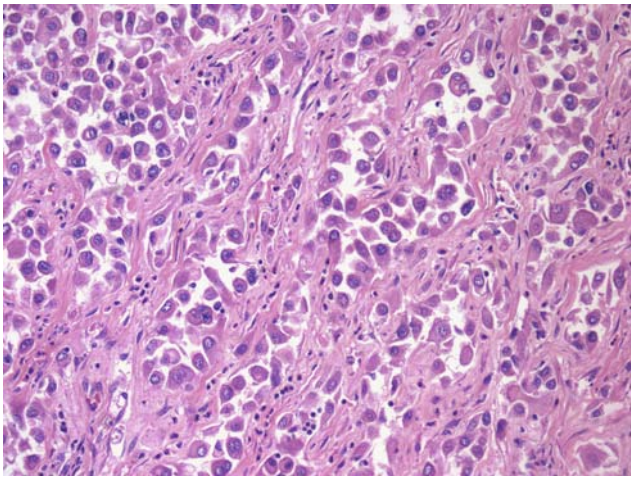

FIGURE 6. Rhabdoid tumor showing a pseudoglandular architecture.

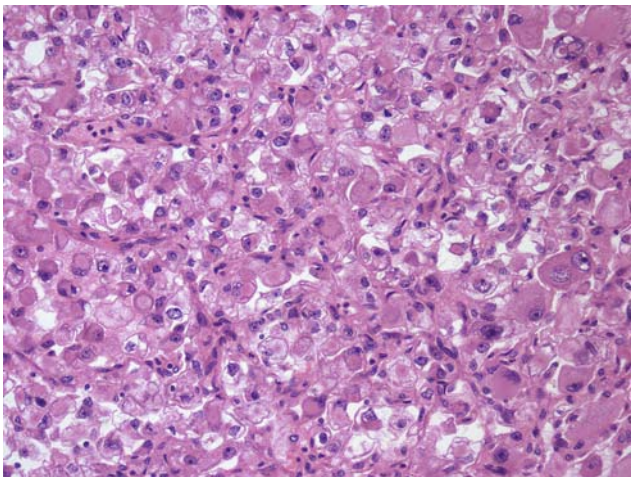

FIGURE 5. Rhabdoid areas of tumor showing a solid growth pattern.

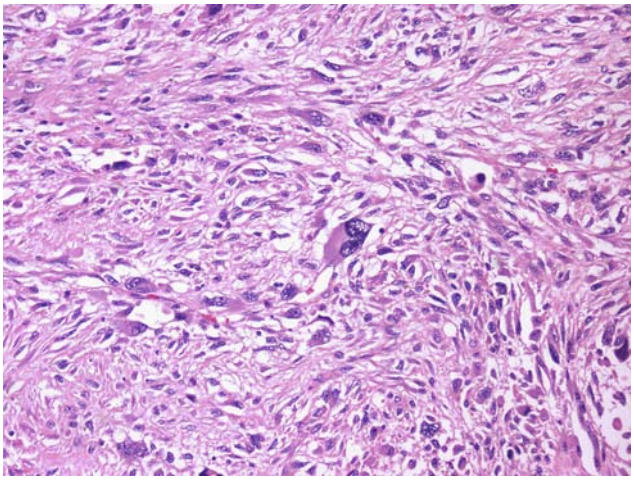

FIGURE 7. Carcinoma and sarcomatoid areas composed of pleomorphic spindle-shaped cells with foci of cells showing rhabdoid morphology.

case reports describe the response to tyrosine kinase inhibitors (sorafenib and sunitinib).[76,78]

Consensus Decisions

The majority of the survey respondents (84%) noted that for tumors with rhabdoid differentiation, they would report the underlying subtype (Table 1). If a tumor shows rhabdoid morphology only, most (85%) respondents would classify this as unclassified carcinoma with a rhabdoid component. Further, the survey indicated only moderate support (61%) for the idea of quantifying the area of rhabdoid differentiation, with the majority (68%) of positive respondents estimating the percentage of such component.

During the meeting, there was consensus (73%) that the presence or absence of rhabdoid differentiation should be specified in the pathology report. A total of 99% of voting delegates agreed that in tumors with rhabdoid differentiation, if there is evidence of histologic type (eg, clear cell RCC), they would diagnose this subtype with rhabdoid differentiation. There was consensus that reporting rhabdoid differentiation should be limited to presence or absence, with little support for reporting the percentage of area involvement.

TUMOR NECROSIS

Tumor necrosis is frequently seen in RCC, being reported from 27% to 31% of cases. The incidence appears to be morphotype dependent, with necrosis being seen in 27% to 32% of clear cell RCC, 32% to 40% of papillary RCC and 3% to 14% of chromophobe RCC.[79–82] This variability may also relate to the definition of tumor necrosis, with some studies relying on the detection of microscopic necrosis and others including tumors showing macroscopic necrosis alone or in combination with microscopic necrosis.

There is uncertainty as to the mechanism by which necrosis develops in RCC. Necrosis may be seen in small tumors, which argues against the probability that necrosis results from tumors growing beyond the supply of existing vasculature.[83] It has been suggested that necrosis has an immune etiology,[84] or results from acute hypoxia due to vascular immaturity[85]; however, a more plausible explanation is that necrosis is due to vascular remodeling that occurs as a tumor progresses in size.[86,87] It is likely that there is a different mechanism associated with the development of necrosis in papillary RCC, and the greater incidence of necrosis seen in these tumors may be because of tumor cell overgrowth, architectural malformation, or susceptibility to trauma.[87]

The prognostic significance of tumor necrosis was first proposed in 1974.[88] Contradictory results have been reported; however, these studies were hampered by the analysis of series containing >1 morphotype of RCC.[89] In subsequent studies the presence of tumor necrosis has been correlated with tumor size, grade, and/or the presence of tumor metastases for clear cell RCC.[4,14,79,80,82,90–98] The presence of tumor necrosis has also been shown to correlate with disease-specific survival both on univariate analysis and multivariate analysis that included tumor size, grade, and the presence of metastases.[4,14,94,95]

In some series no correlation with survival has been demonstrated.[81,83,84,99,100] Some of these series included >1 RCC morphotype or included only small numbers of tumors exhibiting necrosis.[81,99] In studies that included tumors showing extensive necrosis, there was similarly no correlation between the presence of tumor necrosis and survival.[83,84,100,101] Somewhat in contradiction to this, in 1 series of mixed RCC morphotypes, tumors with >50% necrosis were shown to have a less favorable disease-specific survival.[80] In most reports the assessment of tumor necrosis is confined to the identification of microscopic coagulative necrosis, and the possibility arises that when extensive, necrosis has a different pathogenesis, possibly resulting from infarction secondary to large vessel obstruction. In view of this, it has been recommended that a rigorous definition of tumor necrosis should be applied. In particular it has been suggested that assessment should be confined to tumors showing microscopic coagulative necrosis (Fig. 8), with foci of fibrosis, hyalinization, and hemorrhage (Fig. 9) being specifically excluded from consideration.[87,94]

Although there is good evidence to show that tumor necrosis is of prognostic significance for clear cell RCC, it appears that this cannot be applied to all morphotypes of RCC. In particular, most studies relating to papillary RCC show that this parameter does not correlate with survival, probably reflecting the predisposition that these tumors have to undergo spontaneous necrosis.[14,94,102] Studies relating to chromophobe RCC are limited in patient numbers, although for these tumors necrosis has been shown to have prognostic significance on univariate analysis.[94]

Consensus Decisions

In the survey 72% of respondents noted that they reported the presence of coagulative tumor necrosis as a prognostic factor for clear cell RCC. This was also re-

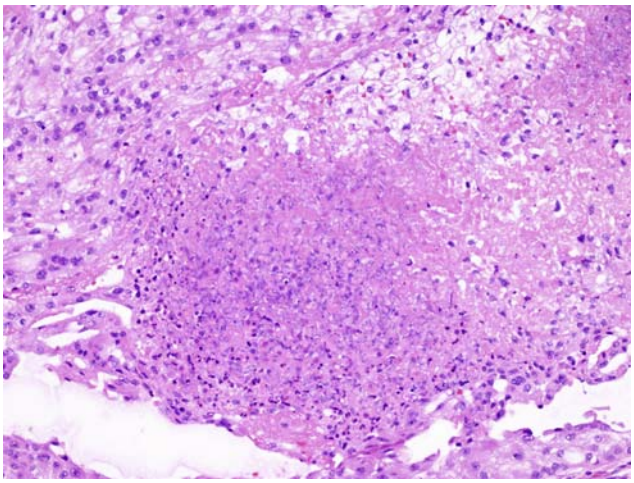

FIGURE 8. Microscopic coagulative necrosis in clear cell RCC.

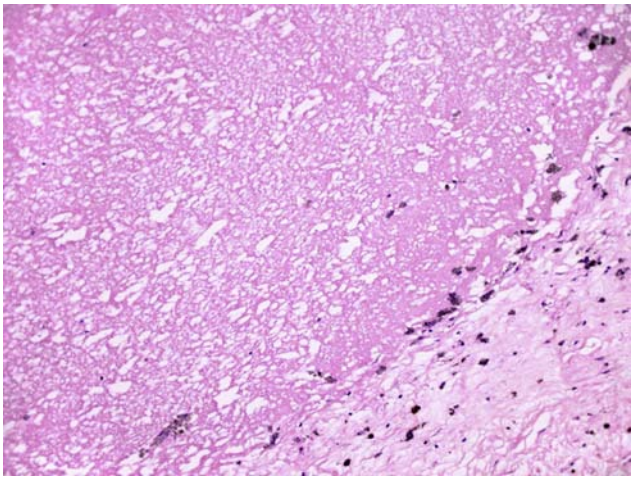

FIGURE 9. Fibrin deposition and fibrosis in low grade carcinoma.

ported for papillary RCC by 54%, for chromophobe RCC by 63%, and for collecting duct carcinoma by 54% of respondents. The area of necrosis was quantified by 50% of respondents, with 52% of these providing a percentage and 55% reporting this as either focal or extensive.

At the conference there was consensus (86%) that, for clear cell RCC, the presence or absence of tumor necrosis should be routinely included in routine pathology reports. It was agreed upon by a consensus (78%) that as our understanding of the prognostic significance of tumor necrosis is in evolution, assessment should include both macroscopic and microscopic examination. For clear cell RCC there was also consensus (69%) that the amount of necrosis present should be recorded as a percentage. Two percent of conference participants considered that the percentage should be determined by examination of gross specimens, whereas 29% considered that microscopic examination of the sections was sufficient.

TUMOR GRADING

The earliest reports on grading of RCC appeared in 1932 by Hand and Broders, and in 1949 by Griffiths and Thackray.[103,104] These workers were the first to identify an association between tumor differentiation and patient outcome. Over 20 years passed before Skinner et al[105] reported on several landmark observations in the grading of RCC. In a series of 309 patients uniformly treated by nephrectomy and followed up for over 6 years, they reported a significant association of 4 grades and 1-, 5-, and 10-year survival rates. Skinner and colleagues defined several histologic parameters in grading RCC, which remain in use today. Their study was the first to grade RCC on the basis of nuclear features alone and to define the grade of RCC on the basis of the highest-grade area within a tumor. In addition, they were the first to associate cell types (or subtypes) with patient outcome. They defined tumors as pure clear, clear and/or granular, and spindle cell (sarcomatoid) and showed that patients with pure clear cell RCC had a significantly better outcome compared with patients with clear cell/granular tumors and that both did significantly better than patients with spindle cell tumors. Although they reported on cell types, they specifically noted that the understanding of RCC types was limited and required further study. Since these studies, several composite grading systems for RCC have been proposed, being based on a variety of morphologic features including tumor architecture, mitotic rate, cellular morphology, and nuclear pleomorphism, whereas more recently novel grading systems have focused on nuclear features alone.[3]

In 1982, Fuhrman et al[106] reported on 105 patients with RCC treated between 1961 and 1974. Of these 105 patients, only 85 had at least 5-year follow-up data, and 84 were treated surgically. The grading system used by Fuhrman and colleagues was adapted from the study by Skinner and colleagues. They defined the first 3 grades on nuclear features, and the fourth grade was defined by the presence of nuclear pleomorphism, with the overall grade being based on the highest-grade area. Unlike Skinner and colleagues who identified survival differences between patients in all 4 of their grades, Fuhrman and colleagues identified only 3 groups that differed in outcome—that is, patients with grade 1 tumors, patients with grade 2 and 3 tumors, and patients with grade 4 tumors. In their series, patients with grade 2 and 3 tumors comprised over 75% of the entire study population and had a similar outcome. In addition to the small number of patients with limited follow-up information and lack of standardized treatment, the study considered RCC a single tumor type and therefore combined clear cell, papillary, and chromophobe subtypes in the analysis. Despite these major limitations, the Fuhrman grading system has been widely adopted in clinical practice.[3]

As our knowledge of RCC subtypes has expanded, and larger and more rigorous studies have been applied to RCC, issues with the Fuhrman grading system have arisen. In particular, the Heidelberg and Rochester Consensus Conferences defined the 4 major RCC morphotypes,[21,22] and, over time, additional rarer variants of RCC have been defined[34] (see working group 1 report).[9] As our knowledge of RCC subtypes has grown and larger studies of patients with RCC subtypes have been reported, the prognostic significance of the Fuhrman grading system has come under question, and limitations of the system have been better defined.

Several problems have been identified with Fuhrman grading.[3,107] Although nuclear diameter can be objectively assessed, nucleolar prominence is more subjective; however, criteria for nuclear pleomorphism are poorly defined. In addition, there is no indication within the system regarding the relative importance of each of these features, and no recommendation is given regarding stratification of parameters in those tumors in which contradictory results are obtained. This problem has been recognized, and there is evidence that pathologists attempt to address this by grading on the basis of nucleolar

prominence alone, which does not conform to the grading criteria of the Fuhrman system.[3]

Studies have shown significant variation in the distribution of Fuhrman grades, and the association between grade and outcome also varies, although in the case of clear cell RCC, larger series have reported significant differences in outcome between grades 1 and 2 versus 3 versus 4.[3] Other issues include a lack of definition for the "highest-grade area" and the uncertainty of the relevance of Fuhrman grading for chromophobe RCC and other RCC subtypes.

Recently, grading systems relying solely on nucleolar prominence have shown a stronger association with patient outcome compared with those relying on Fuhrman grade for clear cell and papillary RCC. In particular, it has been shown that a focal or worse nucleolar grade is superior to the other features of Fuhrman grading criteria for papillary and clear cell RCC, indicating that nucleolar prominence alone is a valid grading system for these tumors.[108,109] In addition, studies have shown that, given the inherent nuclear atypia of chromophobe RCC, Fuhrman grading is inappropriate.[110] This conclusion is supported by the observation that the distribution of the 4 Fuhrman grades reported in chromophobe RCC varies widely between series.[3] Alternative grading systems have been proposed for this morphotype, although the predictive significance of these have not been independently validated and shown to be independent of stage.[42,56,111]

Consensus Decisions

In the survey (Table 2), questions relating to grading focused on current practice. Consensus responses showed that Fuhrman grading was in widespread use, especially for clear cell RCC, multilocular cystic RCC, papillary RCC, and unclassified carcinomas. There was consensus that the highest grade should be reported (83%), although there was no consensus as to the minimum area of tumor that should be assessed for grading purposes. The majority of respondents placed most emphasis on nucleolar prominence for determining the grade.

At the consensus conference a novel grading system (the ISUP grading system) was proposed (Fig. 10). In this system, ISUP grade 1 tumors were defined as having inconspicuous or absent nucleoli at ×400 magnification; for ISUP grade 2 tumors, nucleoli should be distinctly visible at ×400, but inconspicuous or invisible at ×100 magnification; and for ISUP grade 3 tumors, nucleoli should be distinctly visible at ×100 magnification. ISUP grade 4 tumors should encompass tumors with rhabdoid or sarcomatoid differentiation or those containing tumor giant cells or showing extreme nuclear pleomorphism with clumping of chromatin.

There was consensus that this grading system should be applied to clear cell RCC (78%) and papillary RCC (84%). There was also consensus (78%) that, until further data accumulate, chromophobe RCC should not be graded. At the consensus conference the addition of necrosis as a grading parameter was also proposed, and in a study based on 3017 cases, this was shown to be of greater prognostic significance than the proposed ISUP grading system for clear cell RCC. In this study the prognostic significance of grading was retained when cases were stratified for the pT staging category.[87] It was agreed upon that, although this composite grading system appeared very promising, it required further validation by confirmatory studies.

TABLE 2. Survey Results Relating to Grading Practices

	Positive	Responses
What system do you use for grading RCC?		206*
Fuhrman	96	
WHO	7	
Broder	0.5	
Japanese	2	
Nucleolar	11	
Other	2	
Do you provide a grade for		204*
Clear cell RCC	100	
Multilocular cystic RCC	67	
Papillary adenoma	5	
Papillary RCC	85	
Chromophobe RCC	57	
Oncocytoma	1	
Collecting duct carcinoma	41	
Renal medullary carcinoma	31	
Translocation carcinoma	50	
Mucinous tubular spindle cell carcinoma	37	
Tubulocystic carcinoma	37	
End-stage renal disease–associated carcinoma	52	
Unclassified carcinoma	66	
How do you assess Fuhrman grade?		204
Most frequent (1°) pattern	2	
Highest grade	83	
Combined most frequent and highest grade	13	
Provide % of each grade present	2	
What is the minimum area of tumor assessed for grading purposes?		194
1 low-power field (×10 objective)	37	
1 high-power field (×40 objective)	41	
5 high-power fields	10	
Other	12	
For Fuhrman grading do you evaluate?		205*
Nucleolar prominence	99	
Nuclear shape	57	
Nuclear pleomorphism	79	
In case of discordance, which parameter do you put most emphasis on?		205
Nucleolar prominence	68	
Nuclear shape	2	
Nuclear pleomorphism	28	
None	2	

*Answer to >1 option permitted.

MICROVASCULAR INVASION

RCC is one of the most highly vascularized tumors and a characteristic feature of clear cell RCC is the presence of branching, thin-walled vessels among nests and cords of tumor cells. In view of this, it is not surprising that vascular invasion is frequently found in these tumors. Microscopic venous invasion (MVI) has been reported in 5.6% to 45% of RCCs[112–121] and in a recent large study was reported in 18% of a mixed series of RCC.[122] There are several explanations as to the highly variable rate of MVI in these reports. In some series advanced tumor stages were

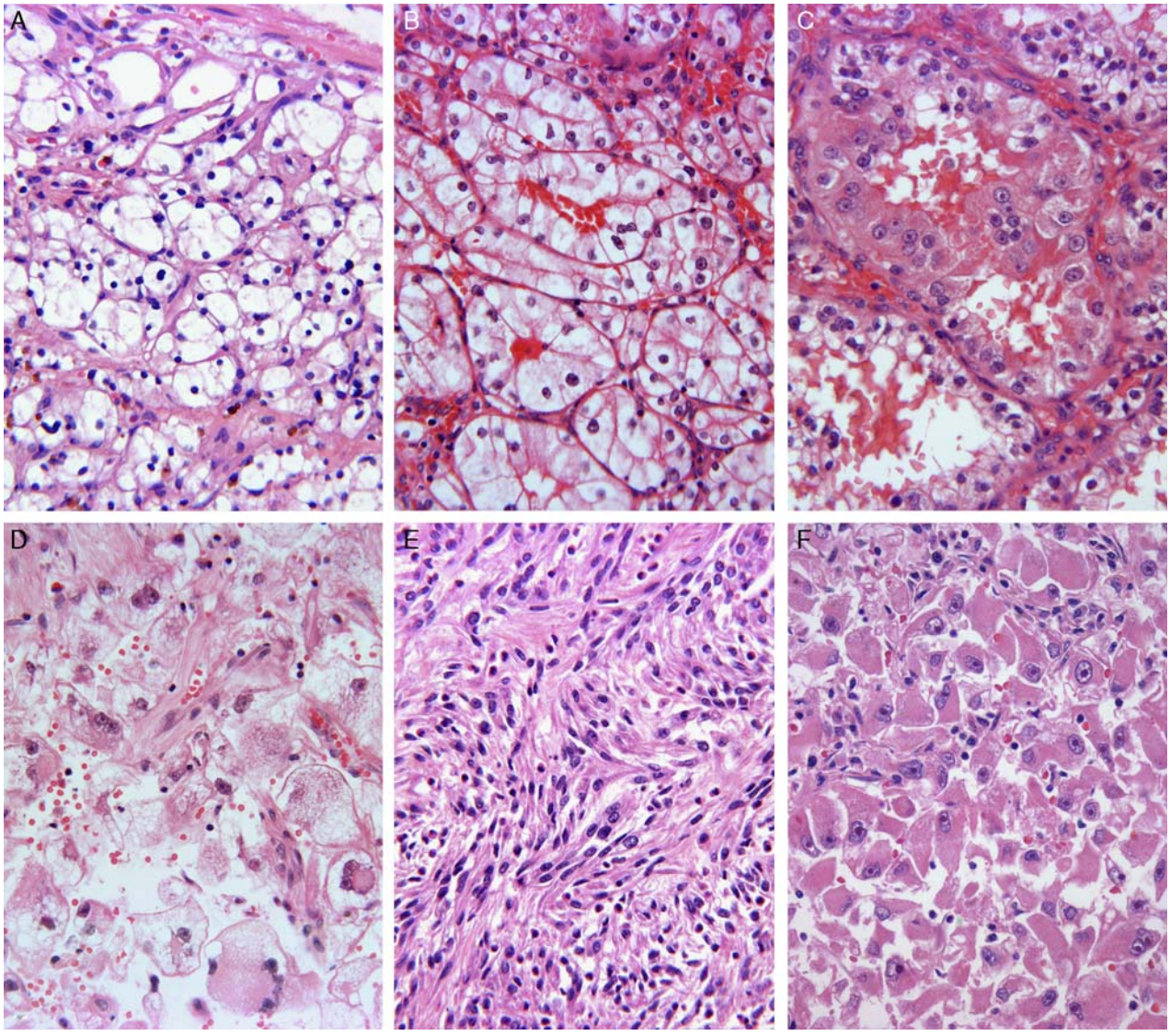

FIGURE 10. The ISUP grading system for clear cell and papillary RCC. A, Grade 1: nucleoli are inconspicuous or absent. B, Grade 2: nucleoli are clearly visible at high-power magnification but are not prominent. C, Grade 3: nucleoli are prominent and are easily visualized at low-power magnification. D, Grade 4: presence of tumor giant cells and/or marked nuclear pleomorphism. E, Grade 4: sarcomatoid carcinoma. F, Grade 4: carcinoma showing rhabdoid differentiation.

included,[115] whereas others included only pT1-2 cancers.[112,116] In some series no account was taken of the tumor morphotype,[113,114,117,122] whereas others focused only on clear cell RCC.[24] Perhaps most importantly, some series were based on centralized review,[113,115] whereas others relied upon data from pathology reports, without formal review.[120,122,123] Notably, the lowest rate of MVI (5.6%) was reported by Pichler et al[123] who only used data from original reports. From these results it would appear that the rate of MVI is dependent on how meticulously slides are reviewed, and as a consequence centralized review will reasonably detect more MVI than seen in routine reporting. In addition, the utilization of immunohistochemical staining increases detection, as this resulted in an MVI rate of 29% in a series of 255 cases.[115]

In some studies, MVI has been found to be a predictor of cancer-specific survival and metastasis-free survival on multivariate analyses that included patient age, tumor size, tumor grade, and capsular penetration.[115,116,118,119,123] Other investigators have failed to demonstrate the value of MVI as a prognostic factor. Cho et al[112] found that MVI predicted recurrence-free survival in univariate, but not in multivariate, analysis, whereas cancer-specific survival was not predicted even in univariate analysis. In a further small study of only 41 cases, MVI was shown not to be an independent predictor of progression-free survival.[121]

More recently in a large study of nonreviewed cases, MVI was correlated with patient age, performance status, tumor diameter, tumor stage and grade, and the presence of lymph node and distant metastases.[122] In this study

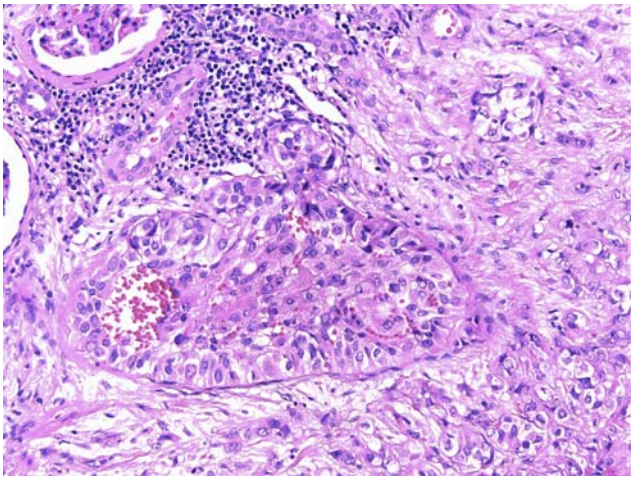

FIGURE 11. A small vessel within the renal parenchyma showing microvascular invasion by clear cell RCC.

MVI correlated with survival on univariate analysis but not on multivariate analysis.

Similar results were obtained from a series of 157 localized RCCs treated by radical surgery.[114] MVI was found in 44.6% of tumors, being seen in 24.7% of patients with tumor recurrence and 17.1% of those who died with cancer progression, which compared with 6.9% and 3.5%, respectively, for tumors without MVI. Despite these differences, MVI was found not to predict outcome on multivariate analysis.

Consensus Decisions

In the survey, MVI was defined by the majority of respondents (82%) as a tumor within small vessels, within the renal parenchyma adjacent to the tumor, or within the tumor pseudocapsule (Fig. 11). The remainder preferred to confine the definition to tumor within small vessels inside the tumor itself. The majority of respondents (72%) noted that they reported the presence of intrarenal MVI as a potential prognostic parameter.

At the consensus conference, the opinion was expressed that there was insufficient evidence at present to promote MVI as a prognostic factor. There was no consensus that reporting of MVI in RCC should be obligatory, although 59% of respondents were in favor of this suggestion. There was consensus (87%) that at present MVI should not be included in TNM staging of RCC.

REFERENCES

1. Srigley JR, Hutter RVP, Gelb AB, et al. Current prognostic factors – renal cell carcinoma. *Cancer*. 1997;80:993–996.
2. Gudbjartsson T, Hardarson S, Petursdottir V, et al. Histological subtyping and nuclear grading of renal cell carcinoma and their implications for survival: a retrospective nation-wide study of 629 patients. *Eur Urol*. 2005;48:593–600.
3. Delahunt B. Advances and controversies in grading and staging of renal cell carcinoma. *Mod Pathol*. 2009;22:S24–S36.
4. Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcomes and prognostic feature among histological subtypes of renal cell carcinoma. *Am J Surg Pathol*. 2003;27:612–624.
5. Delahunt B, Bethwaite PB, Nacey JN. Outcome prediction for renal cell carcinoma: evaluation of prognostic factors for tumours divided according to histological subtype. *Pathology*. 2007;39:459–465.
6. Ficarra V, Martignoni G, Maffei N, et al. Original and reviewed nuclear grading according to the Fuhrman system: a multivariate analysis of 388 patients with conventional renal cell carcinoma. *Cancer*. 2005;103:68–75.
7. Delahunt B, Egevad L, Montironi R, et al. International Society of Urological Pathology (ISUP) consensus conference on renal neoplasia: rationale and organization. *Am J Surg Pathol*. 2013;37:1463–1468.
8. Egevad L, Srigley JR, Delahunt B. International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens: rationale and organization. *Mod Pathol*. 2011;24:1–5.
9. Srigley JR, Delahunt B, Eble JN, et al. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. *Am J Surg Pathol*. 2013;37:e12–e32.
10. Trpkov K, Grignon DJ, Bonsib SM, et al. Handling and staging of renal cell carcinoma: the International Society of Urological Pathology (ISUP) recommendations. *Am J Surg Pathol*. 2013;37:e48–e60.
11. Tan PH, Cheng L, Rioux-Leclercq N, et al. Renal tumors: diagnostic and prognostic markers. *Am J Surg Pathol*. 2013; 37:e61–e74.
12. Mostofi FK. *Histological Typing of Kidney Tumours. World Health Organization*. Geneva: International Histological Classification of Tumours No. 25; 1981.
13. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon: IARC Press; 2004.
14. Moch H, Gasser T, Amin MB, et al. Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors. *Cancer*. 2000;89:604–614.
15. Amin MB, Amin MB, Tamboli P, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms. *Am J Surg Pathol*. 2002;26:281–291.
16. Beck SD, Patel MI, Snyder ME, et al. Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma. *Ann Surg Oncol*. 2004;11:71–77.
17. Ficarra V, Martignoni G, Alfano G, et al. Prognostic role of the histologic subtypes of renal cell carcinoma after slide revision. *Eur Urol*. 2006;50:786–794.
18. Patard JJ, Leray E, Rioux-Leclerq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol*. 2005;23:2763–2767.
19. Capitanio U, Cloutier V, Zini L, et al. A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. *BJU Int*. 2009;103:1496–1500.
20. Novara G, Ficarra V, Antonelli A, et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? *Eur Urol*. 2010;58:588–595.
21. Kovacs G, Akhtar M, Beckwith JB, et al. The Heidelberg classification of renal cell tumours. *J Pathol*. 1997;183:131–133.
22. Störkel S, Eble JN, Adlakha K, et al. Classification of renal carcinoma. *Cancer*. 1997;80:987–989.
23. Leibovich BC, Lohse CM, Crispen PL, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. *J Urol*. 2010;183:1309–1316.
24. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Mod Pathol*. 1997;10:537–544.
25. Gunawan B, von HA, Fritsch T, et al. Cytogenetic and morphologic typing of papillary renal cell carcinomas: evidence for a cytogenetic evolution of type 2 from type 1 tumors. *Cancer Res*. 2003;63:6200–6205.
26. Pignot G, Elie C, Conquy S, et al. Survival analysis of 130 patients with papillary renal cell carcinomas: prognostic utility of type 1 and type 2 subclassification. *Urology*. 2007;69:230–235.

27. Delahunt B, Eble JN, McCredie MRE, et al. Morphological typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. *Hum Pathol*. 2001;32:590–595.
28. Mejean A, Hopirtean V, Bazin JP, et al. Prognostic factors for the survival of patients with papillary renal cell carcinoma: meaning of histological typing and multifocality. *J Urol*. 2003;170:764–767.
29. Waldert M, Haitel A, Marberger M, et al. Comparison of type I and II papillary renal cell carcinoma (RCC) and clear cell RCC. *BJU Int*. 2008;102:1381–1384.
30. Sukov WR, Lohse CM, Leibovich BC, et al. Clinical and pathological features associated with prognosis in patients with papillary renal cell carcinoma. *J Urol*. 2012;187:54–59.
31. Tickoo SK, Reuter VE. Differential diagnosis of renal tumors with papillary architecture. *Adv Anat Pathol*. 2011;18:120–132.
32. Tokuda N, Naito S, Matsuzaki O, et al. Collecting duct (Bellini duct) renal cell carcinoma: a nationwide survey in Japan. *J Urol*. 2006;176:40–43.
33. Wright JL, Risk MC, Hotaling J, et al. Effect of collecting duct histology on renal cell cancer outcome. *J Urol*. 2009;182:2595–2599.
34. Srigley JR, Delahunt B. Uncommon and recently described renal carcinomas. *Mod Pathol*. 2009;22:S2–S23.
35. Aydin H, Chen L, Cheng L, et al. Clear cell tubulopapillary renal cell carcinoma: a study of 36 distinctive low-grade epithelial tumors of the kidney. *Am J Surg Pathol*. 2010;34:1608–1621.
36. Abel EJ, Carrasco A, Culp SH, et al. Limitations of preoperative biopsy in patients with metastatic renal cell carcinoma: comparison to surgical pathology in 405 cases. *BJU Int*. 2012;110:1742–1746.
37. Baer SC, RO JY, Ordonez NG, et al. Sarcomatoid collecting duct carcinoma: a clinicopathologic and immunohistochemical study of five cases. *Hum Pathol*. 1993;24:1017–1022.
38. Bostrom AK, Moller C, Nilsson E, et al. Sarcomatoid conversion of clear cell renal cell carcinoma in relation to epithelial-to-mesenchymal transition. *Hum Pathol*. 2012;43:708–719.
39. Brunelli M, Gobbo S, Cossu-Rocca P, et al. Chromosomal gains in the sarcomatoid transformation of chromophobe renal cell carcinoma. *Mod Pathol*. 2007;20:303–309.
40. Cangiano T, Liao J, Naitoh J, et al. Sarcomatoid renal cell carcinoma: biologic behavior, prognosis, and response to combined surgical resection and immunotherapy. *J Clin Oncol*. 1999;17:523–528.
41. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma. An examination of underlying histologic subtype and an analysis of associations with patient outcome. *Am J Surg Pathol*. 2004;28:435–441.
42. Cheville JC, Lohse CM, Sukov WR, et al. Chromophobe renal cell carcinoma: the impact of tumor grade on outcome. *Am J Surg Pathol*. 2012;36:851–856.
43. Delahunt B. Sarcomatoid renal carcinoma: the final common dedifferentiation pathway of renal epithelial malignancies. *Pathology*. 1993;31:185–190.
44. Delahunt B, Bethwaite PB, McCredie MR, et al. The evolution of collagen expression in sarcomatoid renal cell carcinoma. *Hum Pathol*. 2007;38:1372–1377.
45. de Peralta-Venturina M, Moch H, Amin M, et al. Sarcomatoid differentiation in renal cell carcinoma. A study of 101 cases. *Am J Surg Pathol*. 2001;25:275–284.
46. Dhillon J, Amin MB, Selbs E, et al. Mucinous tubular and spindle cell carcinoma of the kidney with sarcomatoid change. *Am J Surg Pathol*. 2009;33:44–49.
47. Farrow GM, Harrison EG, Utz DC. Sarcomas and sarcomatoid and mixed malignant tumors of the kidney in adults. Part III. *Cancer*. 1968;22:556–563.
48. Jiang F, Moch H, Richter J, et al. Comparative genomic hybridization reveals frequent chromosome 13q and 4q losses in renal carcinomas with sarcomatoid transformation. *J Pathol*. 1998;185:382–388.
49. Jones TD, Eble JN, Wang M, et al. Clonal divergence and genetic heterogeneity in clear cell renal cell carcinomas with sarcomatoid transformation. *Cancer*. 2005;104:1195–1203.
50. Kuroda N, Tamura M, Hamaguschi N, et al. Acquired cystic disease-associated renal cell carcinoma with sarcomatoid change and rhabdoid features. *Ann Diagn Pathol*. 2011;15:462–466.
51. Li YF, Cha TL, Jin JS, et al. Chromophobe renal cell carcinoma with osteosarcoma differentiation: case report and literature review. *Urol Int*. 2010;85:470–474.
52. Mian BM, Bhadkamkar N, Slaton JW, et al. Prognostic factors and survival of patients with sarcomatoid renal cell carcinoma. *J Urol*. 2002;167:65–70.
53. Molina AM, Tickoo SK, Ishill N, et al. Sarcomatoid-variant renal cell carcinoma: treatment outcome and survival in advanced disease. *Am J Clin Oncol*. 2011;34:454–459.
54. Murphy WM, Grignon DJ, Perlman EJ. Kidney tumors in adults, Chapter 2. *Tumors of the Kidney, Bladder and Related Urinary Structures. AFIP Atlas of Tumor Pathology, Series 4*. Washington, DC: American Registry of Pathology; 2004:145–148.
55. Pagliaro LC, Tannir N, Sicar K, et al. Systemic therapy for sarcomatoid renal cell carcinoma. *Expert Rev Anticancer Ther*. 2011;11:913–920.
56. Przybycin CG, Cronin AM, Darvishian F, et al. Chromophobe renal cell carcinoma: a clinicopathologic study of 203 tumors in 200 patients with primary resection at a single institution. *Am J Surg Pathol*. 2011;35:963–970.
57. Quiroga-Garza G, Khurana H, Shen S, et al. Sarcomatoid chromophobe renal cell carcinoma with heterologous sarcomatoid elements. A case report and review of the literature. *Arch Pathol Lab Med*. 2009;133:1857–1860.
58. Ro JY, Ayala AG, Sella A, et al. Sarcomatoid renal cell carcinoma: clinicopathologic: a study of 42 cases. *Cancer*. 1987;59:516–526.
59. Shuch B, Bratslavsky G, Linehan WM, et al. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. *Oncologist*. 2012;17:46–54.
60. Shuch B, Bratslavsky G, Shih J, et al. Impact of pathological tumor characteristics in patients with sarcomatoid renal cell carcinoma. *BJU Int*. 2012;109:1600–1606.
61. Srigley JR, Amin MB, Delahunt B, et al. Protocol for examination of specimens from patients with invasive carcinoma of renal tubular origin. *Arch Pathol Lab Med*. 2010;134:e25–e30.
62. Tomera KM, Farrow GM, Lieber MM. Sarcomatoid renal carcinoma. *J Urol*. 1983;130:657–659.
63. Gokden N, Nappi O, Swanson PE, et al. Renal cell carcinoma with rhabdoid features. *Am J Surg Pathol*. 2000;24:1329–1338.
64. Perez-Montiel MD, Frankel WL, Suster P, et al. Neuroendocrine carcinomas of the pancreas with 'Rhabdoid' features. *Am J Surg Pathol*. 2003;27:642–649.
65. Cheng JX, Tretiakova M, Gong C, et al. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. *Mod Pathol*. 2008;21:647–652.
66. Kuroiwa K, Kinoshita Y, Shiratsuchi H, et al. Renal cell carcinoma with rhabdoid features: an aggressive neoplasm. *Histopathology*. 2002;41:538–548.
67. Shannon B, Wisniewski ZS, Bentel J, et al. Adult rhabdoid renal cell carcinoma. *Arch Pathol Lab Med*. 2002;126:1506–1510.
68. Leroy X, Zini L, Buob L, et al. Renal cell carcinoma with rhabdoid features: an aggressive neoplasm with overexpression of p53. *Arch Pathol Lab Med*. 2007;31:102–106.
69. Weeks DA, Beckwith JB, Mierau GW, et al. Renal neoplasms mimicking rhabdoid tumor of kidney. A report from the National Wilms' Tumor Study Pathology Center. *Am J Surg Pathol*. 1991;15:1042–1054.
70. Shannon BA, Cohen RJ. Rhabdoid differentiation of chromophobe renal cell carcinoma. *Pathology*. 2003;35:228–230.
71. Sukov WR, Cheville JC, Lager DJ, et al. Malignant mixed epithelial and stromal tumor of the kidney with rhabdoid features: report of a case including immunohistochemical, molecular genetic studies and comparison to morphologically similar renal tumors. *Hum Pathol*. 2007;38:1432–1437.
72. Humphrey PA. Renal cell carcinoma with rhabdoid features. *J Urol*. 2011;186:675–676.
73. Ma J, Zhou XJ, Huang WB, et al. Clinicopathologic study of renal cell carcinoma with rhabdoid features. *Zhonghua Bing Li Xue Za Zhi*. 2007;36:166–170.
74. Chapman-Fredricks JR, Herrera L, Brancho J, et al. Adult renal cell carcinoma with rhabdoid morphology represents a neoplastic

dedifferentiation analogous to sarcomatoid carcinoma. *Ann Diagn Pathol*. 2011;15:333–337.
75. Klimis T, Karvounis H. Renal cell carcinoma with rhabdoid features. divergent differentiation of conventional (clear cell) carcinoma. *J BUON*. 2008;13:433–436.
76. Kapoor A, Tutino R, Kanaroglou A, et al. Treatment of adult rhabdoid renal cell carcinoma with sorafenib. *Can Urol Assoc J*. 2008;2:631–634.
77. Shen R, Wen P. Clear cell renal cell carcinoma with syncytial giant cells: a case report and review of the literature. *Arch Pathol Lab Med*. 2004;128:1435–1438.
78. De Vincenzo F, Zucali PA, Corenzi E, et al. Response to sunitinib in an adult patient with rhabdoid renal cell carcinoma. *J Clin Oncol*. 2011;29:e529–e531.
79. Lee SE, Byun SS, Oh JK, et al. Significance of macroscopic tumor necrosis as a prognostic indicator for renal cell carcinoma. *J Urol*. 2006;176:1332–1338.
80. Katz MD, Serrano MF, Grubb RL III, et al. Percent microscopic tumor necrosis and survival after curative surgery for renal cell carcinoma. *J Urol*. 2010;183:909–914.
81. Isbarn H, Patard JJ, Lughezzani G, et al. Limited prognostic value of tumor necrosis in patients with renal cell carcinoma. *Urology*. 2010;75:1378–1384.
82. Pichler M, Hutterer GC, Chromecki TF, et al. Histologic tumor necrosis is an independent prognostic indicator for clear cell and papillary renal cell carcinoma. *Am J Clin Pathol*. 2012;137:283–289.
83. Brinker DA, Amin MB, de Peralta-Venturina M, et al. Extensively necrotic cystic renal cell carcinoma: a clinicopathologic study with comparison to other cystic and necrotic renal cancers. *Am J Surg Pathol*. 2000;24:988–995.
84. Faria V, Surendra T, Poller DN. Prognostic relevance of extensive necrosis in renal cell carcinoma. *J Clin Pathol*. 2005;58:39–43.
85. Hemmerlein B, Kugler A, Ozisik R, et al. Vascular endothelial growth factor expression, angiogenesis, and necrosis in renal cell carcinomas. *Virchows Arch*. 2001;439:645–652.
86. Delahunt B, Bethwaite PB, Thornton A. Prognostic significance of microscopic vascularity for clear cell renal cell carcinoma. *Br J Urol*. 1997;80:401–404.
87. Delahunt B, McKenney JK, Lohse CM, et al. A novel grading system for clear cell renal cell carcinoma incorporating tumor necrosis. *Am J Surg Pathol*. 2013;37:311–322.
88. Amtrup F, Hansen JB, Thybo E. Prognosis in renal carcinoma evaluated from histological criteria. *Scand J Urol Nephrol*. 1974;8:198–202.
89. Delahunt B, Nacey JN. Renal cell carcinoma: histological indicators of prognosis. *Pathology*. 1987;19:258–263.
90. Lam JS, Shvarts O, Said JW, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. *Cancer*. 2005;103:2517–2525.
91. Cheville JC, Blute ML, Zincke H, et al. Stage pT1 conventional (clear cell) renal cell carcinoma: pathological features associated with cancer specific survival. *J Urol*. 2001;166:453–456.
92. Frank I, Blute ML, Cheville JC, et al. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*. 2002;168:2395–2400.
93. Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer*. 2003;97:1663–1671.
94. Sengupta S, Lohse CM, Leibovich BC, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. *Cancer*. 2005;104:511–520.
95. Ficarra V, Martignoni G, Lohse C, et al. External validation of the Mayo Clinic Stage, Size, Grade and Necrosis (SSIGN) score to predict cancer specific survival using a European series of conventional renal cell carcinoma. *J Urol*. 2006;175:1235–1239.
96. Thompson RH, Leibovich BC, Lohse CM, et al. Dynamic outcome prediction in patients with clear cell renal cell carcinoma treated with radical nephrectomy: the D-SSIGN score. *J Urol*. 2007;177:477–480.
97. Tollefson MK, Thompson RH, Sheinin Y, et al. Ki-67 and coagulative tumor necrosis are independent predictors of poor outcome for patients with clear cell renal cell carcinoma and not surrogates for each other. *Cancer*. 2007;110:783–790.
98. Zubac DP, Bostad L, Gestblom C, et al. Renal cell carcinoma: a clinicopathological follow-up study after radical nephrectomy. *Scand J Urol Nephrol*. 2007;41:191–197.
99. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol*. 2005;173:48–51.
100. Klatte T, Remzi M, Zigeuner RE, et al. Development and external validation of a nomogram predicting disease specific survival after nephrectomy for papillary renal cell carcinoma. *J Urol*. 2010;184:53–58.
101. Minervini A, Di Cristofano C, Gacci M, et al. Prognostic role of histological necrosis for nonmetastatic clear cell renal cell carcinoma: correlation with pathological features and molecular markers. *J Urol*. 2008;180:1284–1289.
102. Kim H, Cho NH, Kim DS, et al. Renal cell carcinoma in South Korea: a multicenter study. *Hum Pathol*. 2004;35:1556–1563.
103. Hand JR, Broders AC. Carcinoma of the kidney: the degree of malignancy in relation to factors bearing on prognosis. *J Urol*. 1932;28:199–216.
104. Griffiths IH, Thackray AC. Parenchymal carcinoma of the kidney. *Br J Urol*. 1949;21:128–151.
105. Skinner DG, Colvin RB, Vermillion CD, et al. Diagnosis and management of renal cell carcinoma: a clinical and pathologic study of 309 cases. *Cancer*. 1971;28:1165–1177.
106. Fuhrman SA, Lasky LC, Limas C. Prognostic significance in morphologic parameters in renal cell carcinoma. *Am J Surg Pathol*. 1982;6:656–663.
107. Goldstein N. Grading of renal cell carcinoma. *Urol Clin North Am*. 1999;26:637–642.
108. Sika-Paotonu D, Bethwaite PB, McCredie MRE, et al. Nucleolar grade but not Fuhrman grade is applicable to papillary renal cell carcinoma. *Am J Surg Pathol*. 2006;30:1091–1096.
109. Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Grading of clear cell renal cell carcinoma should be based on nucleolar prominence. *Am J Surg Pathol*. 2011;135:1134–1139.
110. Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Fuhrman grading is not appropriate for chromophobe renal cell carcinoma. *Am J Surg Pathol*. 2007;31:957–960.
111. Paner GP, Amin MB, Alvarado-Cabrero I, et al. A novel tumor grading scheme for chromophobe renal cell carcinoma. prognostic utility and comparison with Fuhrman nuclear grade. *Am J Surg Pathol*. 2010;34:1233–1240.
112. Cho HJ, Kim SJ, Ha US, et al. Prognostic value of capsular invasion for localized clear-cell renal cell carcinoma. *Eur Urol*. 2009;56:1006–1012.
113. Griffiths DF, Verghese A, Golash A, et al. Contribution of grade, vascular invasion and age to outcome in clinically localized renal cell carcinoma. *BJU Int*. 2002;90:26–31.
114. Ishimura T, Sakai I, Hara I, et al. Microscopic venous invasion in renal cell carcinoma as a predictor of recurrence after radical surgery. *Int J Urol*. 2004;11:264–268.
115. Lang H, Lindner V, Letourneux H, et al. Prognostic value of microscopic venous invasion in renal cell carcinoma: long-term follow-up. *Eur Urol*. 2004;46:331–335.
116. Madbouly K, Al-Qahtani SM, Ghazwani Y, et al. Microvascular tumor invasion: prognostic significance in low-stage renal cell carcinoma. *Urology*. 2007;69:670–674.
117. Miyagawa T, Shimazui T, Hinotsu S, et al. Does tumor size or microvascular invasion affect prognosis in patients with renal cell carcinoma? *Jpn J Clin Oncol*. 2007;37:197–200.
118. Roos FC, Weirich J, Victor A, et al. Impact of several histopathological prognosticators and local tumour extension on oncological outcome in pT3b/c N0M0 renal cell carcinoma. *BJU Int*. 2009;104:461–469.
119. Van Poppel H, Vandendriessche H, Boel K, et al. Microscopic vascular invasion is the most relevant prognosticator after radical

nephrectomy for clinically nonmetastatic renal cell carcinoma. *J Urol*. 1997;158:45–49.
120. Pichler M, Hutterer GC, Chromecki TF, et al. External validation of the Leibovich prognosis score for nonmetastatic clear cell renal cell carcinoma at a single European center applying routine pathology. *J Urol*. 2011;186:1773–1777.
121. Sevinc M, Kirkali Z, Yorukoglu K, et al. Prognostic significance of microvascular invasion in localized renal cell carcinoma. *Eur Urol*. 2000;38:728–733.
122. Kroeger N, Rampersand EN, Patard JJ, et al. Prognostic value of microvascular invasion in predicting cancer specific survival and risk of metastatic disease in renal cell carcinoma: a multicenter investigation. *J Urol*. 2012;187:418–423.
123. Pichler M, Hutterer GC, Chromecki TF, et al. Prognostic value of the Leibovich prognosis score supplemented by vascular invasion for clear cell renal cell carcinoma. *J Urol*. 2012;187:834–839.

APPENDIX

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