Grading Systems in Renal Cell Carcinoma

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Purpose: We reviewed updated literature data concerning several issues of renal cell carcinoma grading systems.
Materials and Methods: We performed a nonsystematic review of the literature. Data were identified by a MEDLINE® search using a strategy including MeSH® and free text protocols. From the MEDLINE search we collected 184 records.
Results: Although the original study was published in 1982, the independent predictive value of nuclear grades was only revealed in 2000 by the team from University of California-Los Angeles. Subsequently further data from our group and the group at the Mayo Clinic reconfirmed those findings, although similar cancer specific survival probabilities were noted among different grades. The prognostic relevance of nuclear grade justified the inclusion of that variable in algorithms and nomograms predictive of cancer specific survival, such as those provided by University of California-Los Angeles, the Mayo Clinic and Memorial Sloan-Kettering Cancer Center. Despite the routine clinical use of nuclear grade, several drawbacks have affected grading systems, such as interobserver and intra-observer reproducibility, and variability of the cancer specific survival probabilities stratified by grade. Several studies showed that intra-observer and interobserver agreement with regard to grade are only moderate with up shifting in all series. That issue might be due to the heterogeneity of renal cell carcinoma as well as to the lack of consensus about the minimal size of high grade tumor to be considered significant. Moreover, recent data underscore the role of histological subtypes.
Conclusions: Grade is one of the most powerful prognostic factors in patients with renal cell carcinoma. The Fuhrman grading system is currently most widely used by pathologists in Europe and the United States. However, there is still a need for better standardization of nuclear criteria to improve interobserver reproducibility and a major consensus should be achieved by uropathologists.

Key Words: kidney; kidney neoplasms; carcinoma, renal cell; mortality; nomograms

Kidney tumors are the third most frequent genitourinary tract tumor, accounting for 2.6% of all malignancies. In the United States about 38,890 new cases were estimated to be diagnosed during 2006 and 12,840 cancer related deaths were estimated to occur.[1] RCC is the most common pathological diagnosis, accounting for about 90% of all renal neoplasms. Several clinical and pathological prognostic factors have been considered, including ECOG PS, presentation mode, primary tumor pathological stage, lymph node involvement, nuclear grade and carcinoma histological subtype.

We focused on histological grade. Specifically we addressed the most relevant issues concerning nuclear grade in RCC, such as the different grading systems, its correlations with other pathological variables, its clinical relevance, its independent predictive value and its role in nomograms or algorithms predicting outcomes as well as the major drawbacks of all grading systems.

SEARCH STRATEGY

We performed a nonsystematic review of the literature. Data were identified by a MEDLINE search in February 2006 using a strategy including MeSH and free text protocols. Specifically the MeSH search was performed using the search term "carcinoma, renal cell" retrieved from the MeSH browser provided by MEDLINE. A free text search was performed by applying the term nuclear grad* through the title and abstract fields of the records. The MEDLINE searches were pooled to collect 184 records, whose full texts were reviewed by 2 of us (GN and VF). In addition, other significant studies cited in the reference lists of the selected studies were considered.

HISTORICAL PERSPECTIVE

Several grading systems have been proposed based on tumor cell cytoplasmic and/or architectural features. Table 1 lists the characteristics of the different grading systems available for RCC.[2–9]

In 1932 Hand and Broders were the first to report a relationship between histological grade and cancer specific survival in patients with RCC, noting that patients with high grade RCC were more likely to die and they died sooner after diagnosis than those with low grade tumors.[10] After the proposals of Arner et al in 1965,[3] Skinner et al in 1971,[4] and Syrjanen and Hjelt in 1978[5] Fuhrman et al created a new grading system in 1982, which was the most widespread system used worldwide in subsequent years.[6] The system was based exclusively on RCC cell nuclear features. The figure shows conventional RCC Fuhrman grades 1 to 4.

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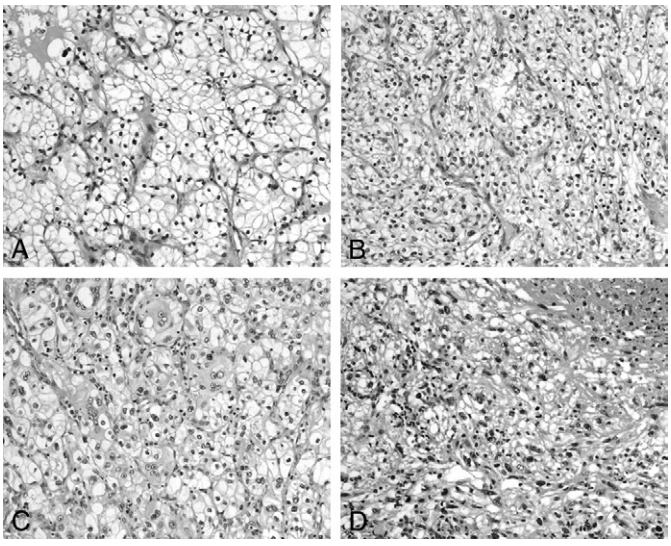
TABLE 1. *Proposed RCC grading systems*[2]

System (grade)	Definition
Arner:[3]	
1	Well differentiated, well demarcated, no polymorphism
2A	Moderately differentiated, locally circumscribed, not necessarily capsulated
2B	Poorly circumscribed but not infiltrating, marked polymorphism, mitoses present
3	Poorly differentiated, markedly pleomorphous, infiltrating, tumor found in capillaries
Skinner:[4]	
1	Small nuclei indistinguishable from normal tubular cell nuclei
2	Slightly irregular, frequently pyknotic but no nucleoli
3	Large, irregular, pleomorphic nuclei with prominent nucleoli
4	Extremely bizarre nuclei
Syrianen and Hjelt:[5,*]	
1	Spherical nuclei of equal size, delicate chromatin, inconspicuous nucleoli, rare mitoses
2	Slightly larger spherical nuclei with distinct nucleoli + few scattered mitoses
3	Prominent anisonucleosis + nucleoli, frequent mitoses
4	Many bizarre nuclei + frequent mitoses, frequent spindle-shaped cells
Fuhrman nuclear grading:[6]	
1	Tumor cells with small (approximately 10 μm) round uniform nuclei without nucleoli
2	Tumor cells with larger nuclei (approximately 15 μm) with irregularities in outline + nucleoli when examinated under high power (400×)
3	Tumor cells with even larger nuclei (approximately 20 μm) with obviously irregular outline + prominent larger nucleoli even at low power (100×)
4	Tumor cells with bizarre, multilobed nuclei + heavy clumps of chromatin
Thoenes:[7]	
1	Small nuclei similar to normal tubular cell nuclei, chromatic delicate or condensed up to pyknosis
2	Larger nuclei varying moderately in size + shape
3	Highly enlarged nuclei, polymorphous or spindle-shaped, varying in size up to giant nuclei, chromatin highly coarsened, single or multiple nucleoli, mostly extremely enlarged, frequent mitoses, often atypical
Delahunt and Nacey:[8]	
1	Small nucleus uniform in size and shape, small nucleolus, round and basophilic
2	Moderate grade of variation in nucleous size and shape with some angularity of nuclear margins, chromatin clumping at nuclear membrane, brightly eosinophilic nucleolus prominent in nucleus
3	Pronounced variation in nucleus size with giant forms +/or multinucleate tumor giant cells, large + angulated nucleolus with multiple nucleoli in same nucleus
Mayo Clinic standardized nuclear grade:[9]	
1	Tumor cells with small round nuclei with inconspicuous nucleoli (visible at 400×)
2	Tumor cells with round to slightly irregular nuclei with mildly enlarged nucleoli (visible at 200×)
3	Tumor cells with round to irregular nuclei with prominent nucleoli (visible at 100×)
4	Tumor cells with enlarged, pleomorphic or giant cells

* Each category is divided into A—well and B—poorly demarcated.

PROGNOSTIC ROLE OF NUCLEAR GRADING SYSTEMS

Most pathologists in the United States currently use the Fuhrman grading system.[11] Several published studies analyzing the prognostic value and reproducibility of grading systems for RCC used the Fuhrman system. In their cohort of 103 patients with RCC Fuhrman et al found that grade 1 tumors had a statistically significantly lower metastasis rate compared to that of grades 2 to 4 tumors.[6] Moreover, reported 5-year overall survival rates were 64%, 34%, 31% and 10% for grades 1 through 4, respectively. Hence, in terms of survival the system distinguished 3 categories of patients, including those with a favorable prognosis (grade 1), those with a poor prognosis (grade 4) and a large group that was between grades 1 and 4 (grades 2 and 3). Although survival rates in patients with grades 2 and 3 disease overlapped, the investigators elected to separate them because of the clearly distinct nuclear morphology, considering that larger series with longer followup would have shown a significant survival difference between grades 2 and 3 tumors.[6] Methodologically the dimension of the patient sample, the use of different therapies for the kidney cancer, the presence of different histological subtypes and the use of overall rather than cancer specific survival strongly limited the clinical relevance of the study.



Clear cell RCC. *A*, Fuhrman grade 1. Reduced from ×20. *B*, Fuhrman grade 2. Reduced from ×10. *C*, Fuhrman grade 3. Reduced from ×10. *D*, Fuhrman grade 4. Reduced from ×10.

Several subsequent groups reported different survival cutoff points and significant survival differences among the different grades. Table 2 lists cancer specific survival probabilities stratified by tumor grade, as reported in the most relevant published studies, as well as the grade groups yielded.[6,12–30]

In one of the most interesting studies Bretheau et al performed a complex analysis in 190 patients with RCC

TABLE 2. *Cancer specific survival probabilities stratified by nuclear grade*

References	No. Pts	Stage	Histological Subtype	% Grade 5-Yr Survival 1	2	3	4	Grade Clustering
Fuhrman et al[6]	103	I–IV	All	65	30	32	10	1 Vs 2–4
Medeiros et al[12]	121	I–IV	All	85	70	21	23	1–2 Vs 3–4
Grignon et al[13]	103	I–IV	All	88		80	43	1–2 Vs 3–4
Green et al[14]	55	I	All		91		9	1–3 Vs 4
Munichor et al[15]	79	I–IV	All	50	55	10.5	14.3	1–2 Vs 3–4
Gelb et al[16]	82	I	All		Not reported			1–2 Vs 3–4
Bretheau et al[17]	190	I–IV	All	76	72	51	35	1–2 Vs 3–4
Usubuton et al[18]	165	I–IV	All	97	83	78	66	1–2 Vs 3–4
Tsui et al[19]	643	I–IV	All	89	65	46		1 Vs 2 vs 3–4
Ficarra et al[20]	333	I–IV	All	94	86	59	31	1–2 Vs 3 vs 4
Frank et al[21]	1,801	I–IV	All		Not reported			1–2 Vs 3 vs 4
Minervini et al[22]	213	I–II	All	96	87	60		1–2 Vs 3–4
Amin et al[23]	405	I–IV	All	100	94	80	35	1–2 Vs 3 vs 4
Ficarra et al[24]	1,446	I–IV	All	86.1	79.7	59.4	29.4	1 Vs 2 vs 3 vs 4
Cheville et al[25]	1,985	I–IV	Clear cell	Not reported	Not reported	Not reported	Not reported	1–2 Vs 3 vs 4
Cheville et al[25]	270	I–IV	Papillary	Not reported	Not reported	Not reported	Not reported	1–2 Vs 3 vs 4
Mejean et al[26]	88	I–IV	Papillary	91		51		1–2 Vs 3–4
Erdogan et al[27]	75	I–IV	All	84.6	60.5	11.5	6.4	1–2 Vs 3–4
Ficarra et al[28,*]	388	I–IV	Clear cell	95.4	90.7	65.3	40	1–2 Vs 3 vs 4
Ficarra et al[28,†]	388	I–IV	Clear cell	100	90.1	77.1	54.7	1–2 Vs 3 vs 4
Patard et al[29]	4,063	I–IV	All	89.1	72.1	49.8	28	1 Vs 2 vs 3 vs 4
Gudbjartsson et al[30]	701	I–IV	All	87.3	70.5	45.9	15.5	Not reported

* Original Fuhrman nuclear grading system.
† Reviewed Fuhrman nuclear grading system.

treated with radical nephrectomy.[17] They noted a statistically significant correlation between the Fuhrman nuclear grading system and the other most relevant pathological variables, including tumor volume, primary tumor pathological stage, extrarenal venous system invasion, lymph node involvement and distant metastases. Of grades 1 and 2 RCCs 80% and 44% were localized vs 41% and 30% of grades 3 and 4 cases, respectively. No grade 1 or 2 RCCs were pN+ vs 12% and 54% of grades 3 and 4 cases, respectively. Only 3% and 4% of patients with grades 1 and 2 disease showed pM+ vs 29% and 54% of those with grades 3 and 4, respectively. Moreover, the investigators found a statistically significant survival difference after clustering grades 1–2 and grades 3–4 RCC, while no significant survival difference was detected after stratifying the subgroup of patients with localized RCC by grade.

In 1997 the UICC and American Joint Committee on Cancer organized the Diagnosis and Prognosis of Renal Cell Carcinoma: 1997 Workshop in Rochester, Minnesota to highlight the state of the art for RCC. The Workgroup No. 2 on RCC grading recognized that most existing grading systems of renal cell carcinoma "likely provided significant prognostic information" when applied by experienced uropathologists but nuclear grading systems were considered more predictive than other grading systems that did not include nuclear criteria.[31] In addition, the Consensus Conference highlighted the controversies of RCC grading, concluding that "an ideal grading system needed to be established" and "a three-grade system was recommended."[31] Thereafter, a few relevant studies were published. In 2000 Tsui et al reported on 643 patients with RCC treated at UCLA with radical and partial nephrectomy, finding significant survival differences between grades 1 and 2, and between grades 2 and 3–4 tumors.[19] In addition, the study confirmed the correlation of nuclear grade and pathological stage with 91% of grade 1 or 2 RCCs in stage I and 61% of grade 3 or 4 cancers in stage IV. In 2001 Ficarra et al analyzed 333 patients who underwent radical nephrectomy for RCC and confirmed the correlation between Fuhrman nuclear grade and other pathological variables, such as primary tumor pathological stage, pathological lymph node involvement, metastases and venous system invasion.[20] Moreover, they observed that the survival probabilities of grades 1 and 2 tumors overlapped, while a significantly different outcome was noted between grades 1–2, 3 and 4 neoplasms. Similar survival rates were reported by Frank et al, who analyzed 1,801 patients treated at the Mayo Clinic for clear cell RCC.[21] At a mean followup of almost 10 years they noted similar survival rates for grades 1 and 2 tumors, which were significantly better than those for grade 3.

No study unequivocally showed the predictive value of nuclear grading systems regardless of pathological tumor stage until 2000, when the UCLA group reported a multivariate analysis of RCC prognostic factors using the Cox proportional hazard model.[19] The investigators generated a multivariate model including ECOG PS, primary tumor stage according to the 1997 TNM staging system, overall TNM pathological stage and nuclear grade. After clustering grades 3 and 4 the Fuhrman nuclear grading system proved to be an independent predictor of cancer specific survival as well as overall 1997 pathological stage (each $p < 0.001$).

In 2001 Ficarra et al reported a multivariate model including only pathological variables.[20] The Fuhrman nuclear grading system proved significant after grouping grades 1 and 2 ($p = 0.002$). T stage ($p < 0.0001$), N stage ($p = 0.009$) and M stage ($p < 0.0001$) were also statistically significant. In 2002 the Mayo Clinic group reported a Cox proportional hazard model using bootstrap methodology.[21] Also, in this study after combining grades 1 and 2 nuclear grading was an independent predictor of cancer specific survival with a risk ratio of 1.50 and 3.01 for grades 3 and 4, respectively (each $p < 0.001$). In these series the prognostic value was identified only after clustering patients into 3 categories. Indeed, in a 4-grade system each grade should identify patients who have a significantly different tumor related outcome and the survival advantage cutoff points should form a continuum.[32]

Only few series have demonstrated the significant prognostic value of the Fuhrman system without clustering groups of patients with different grades. Ficarra et al reported 1,446 RCCs treated with radical nephrectomy and nephron sparing surgery at 2 Italian urological centers, including the University of Verona and University of Padua.[24] Five and 10-year cancer specific survival rates were 86.1% and 77.2% for grade 1, 79.7% and 67.7% for grade 2, 59.4% and 45.9% for grade 3, and 29.4% and 18.5% for grade 4 RCC, respectively. Patients with grade 1 RCC had better survival rates than those with grade 2 ($p = 0.02$). Similarly the curve of grade 2 cancer was significantly different from that of grade 3 ($p < 0.0001$), while the curve of grade 3 was significantly different from that of grade 4 ($p < 0.0001$). Multivariate analysis confirmed the independent predictive value of the Fuhrman nuclear grading system ($p < 0.001$), as well as that of pathological stage ($p < 0.001$), pathological size 4 or less vs more than 4 cm ($p = 0.003$), venous involvement ($p = 0.001$) and presentation mode ($p = 0.001$). However, although the survival difference between grades 1 and 2 tumors was statistically significant, the data might be clinically irrelevant. Univariate analysis demonstrated only a 10% difference in 10-year cancer specific survival, which might have been statistically significant only because of the extremely high number of censored cases rather than because of a clinically relevant difference.

Similarly Patard et al reported a large, multicenter study including more than 4,000 patients from 8 international, academic centers in Europe and the United States.[29] The study focused on assessment of the independent predictive value of tumor histological subtypes. On univariate analysis Fuhrman nuclear grades were statistically significant with 5 and 10-year cancer specific survival rates of 89.1% and 81% for grade 1, 72.1% and 56.5% for grade 2, 49.8% and 30.1% for grade 3, and 28% and 18.8% for grade 4 tumors, respectively ($p = 0.0001$). Moreover, the Fuhrman nuclear grading system was an independent predictor of cancer specific survival on multivariate analysis as well as of TNM stage and ECOG PS.

PREDICTIVE MODELS AND NOMOGRAMS INCLUDING NUCLEAR GRADE

The generation of multivariate models enabled the possibility of weighing the relevance of nuclear grading systems for predicting cancer specific survival independently of the other clinical (PS and presentation mode) and pathological (pathological stage, pathological size and tumor necrosis) variables. Outcome predictive models were developed with the intent to integrate all of these variables in a single algorithm or nomogram, which might allow easy stratification of patients into different prognostic categories. It ultimately could be useful for directing therapy, assessing patient response, determining eligibility for entry into clinical trials and interpreting their results.[33] A few of those prognostic models were developed for patients with RCC, although the statistical analyses that generated the models were always performed in retrospective series of patients with all of the well-known limitations of such approach.

In 2001 Zisman et al reported on 661 patients treated with radical or partial nephrectomy from 1989 to 1999 at UCLA.[33] They used the Fuhrman nuclear grading system, 1997 TNM stage and ECOG PS to generate an integrated staging system (UCLA Integrated Staging System), which stratified patients into 5 prognostic groups. Subsequently the same group proposed 2 simplified algorithms, that is 1 for N0M0, and 1 for N+ and/or M+ RCC, including only 3 risk groups (low, intermediate and high),[34] which were externally validated in 2 independent, multicenter series.[35,36]

In 2002 Frank et al introduced a further model to predict prognosis in patients who undergo radical nephrectomy for conventional RCC.[21] After analyzing a cohort of 1,800 patients treated at the Mayo Clinic the investigators provided the SSIGN score, which is able to estimate 1, 3, 5, 7 and 10-year cancer specific survival based on multivariate analysis indicating that these variables are independent predictor of cancer specific survival. This score is limited to clear cell RCC only and it does not include ECOG PS, which did not prove to be statistically significant even on univariate analysis because more than 90% of patients at the Mayo Clinic had an ECOG score of 0. However, neither model considered the presentation mode of kidney cancer, which is a proven predictor of patient survival.[19,24,37] Recently the SSIGN score was externally validated in the Verona University series.[38] In 2003 the same group reported a surveillance model predicting the probabilities of thoracic, abdominal or bone recurrence-free survival at different times (3 months to 10 years).[39]

Recently Sorbellini et al from Memorial Sloan-Kettering Cancer Center reported a prognostic nomogram predictive of 5-year recurrence-free survival probabilities in patients with conventional RCC.[40] The nomogram included tumor size, primary tumor pathological stage according to the 2002 TNM staging system, nuclear grade, presentation mode and tumor necrosis plus vascular invasion. Table 3 shows proposed RCC predictive models and nomograms.[21,34,39,40]

LIMITATIONS OF GRADING SYSTEMS FOR RCC

Overall reported 5-year cancer specific survival probabilities are extremely variable. When stratifying by grade, the rates are 50% to 100% in grade 1, 30% to 94% in grade 2, 10% to 80% in grade 3 and 9% to 66% in grade 4 tumors (table 2). The wide variability of the reported data could be explained in several ways.

1) Many investigators have pointed out the moderate interobserver reproducibility of the Fuhrman nuclear grading system. Lanigan et al were the first to analyze the level of agreement among 4 pathologists assigning RCC grades according to 4 systems, including the Arner, Skinner, Syrjanen-Hjelt and Fuhrman systems.[2] Using the κ statistic as a measure of agreement among observers, which corrects for chance agreement[41] to evaluate concordance among pathologists, interobserver agreement was shown to be moderate for the Syrjanen-Hjelt, Fuhrman, Skinner and Arner systems ($\kappa = 0.42, 0.33, 0.26$ and 0.24, respectively).[2] In a larger study in the field Lohse et al compared original nuclear grades assigned at initial pathological diagnosis to standardized grades reassigned after slide review in more than 2,000 cases at the Mayo Clinic.[9] The study provided separated analyses for clear cell, papillary and chromophobe RCC. For conventional RCC nuclear grade remained unchanged on review in 56.3% of cases, while it was up shifted in 35.2% by 1 or more grades and down shifted in 8.4%. For the papillary histological subtype 49% of the original grades were reconfirmed, while 44.1% and 6.8% were up and down shifted, respectively. Similarly 55%, 38% and 7% of chromo-

TABLE 3. *RCC predictive models and nomogram*

Predictive Model (categories)	Histological Subtype	Variables	Outcome	External Validation
UCLA integrated staging system, no metastasis (risk):[34]	All	TNM, Fuhrman grade, ECOG PS	1–5-Yr overall + Ca specific survival probability	Yes
Low (T1N0M0, G1–2, ECOG PS 0)				
Intermediate (T1N0MO, G1–2, ECOG PS 1 or greater; T1N0M0, G3–4, any ECOG PS; T2N0M0, any G, any ECOG PS; T3N0M0, G2–4, ECOG PS 0)				
High (T3 G2–4, ECOG PS 1 or greater; T4N0M0, any G, any ECOG PS				
UCLA integrated staging system, metastasis (risk):[34]	All	TNM, Fuhrman grade, ECOG PS	1–5-Yr overall + Ca specific survival probability	Yes
Low (N1M0, any G, any ECOG PS; N2M0–1, G2, ECOG PS 0)				
Intermediate (N2M0–1, G1, ECOG PS 1 or greater; N2M0–1, G3, any ECOG PS; N2M0–1, G4, ECOG PS 0)				
High (N2M0–1, G4, ECOG PS greater than 1)				
Mayo Clinic:				
SSIGN (discrete score 1–15)[21]	Clear cell RCC	TNM stage, size (less than 5 cm vs 5 or greater), nuclear grade, necrosis	1–10-Yr Ca specific survival probability	Yes
Surveillance model (discrete score)[39]	Clear cell RCC	TNM stage, size (less than 10 cm vs 10 or greater), nuclear grade, necrosis, surgical margins	3-Mo–10-yr abdomen, thoracic or bone recurrence-free probability	No
Memorial Sloan-Kettering Cancer Center (continuous prediction via nomogram)[40]	Clear cell RCC	Size, TNM stage, Fuhrman grade, necrosis, vascular invasion, presentation mode	5-Yr recurrence-free probability	No

phobe tumors were confirmed, upgraded and downgraded on review, respectively. More importantly the investigators noted that for each histological subtype the revised nuclear grades were powerful predictors of cancer specific survival, also after adjusting for 1997 TNM stage.

In a similar European study Ficarra et al compared original and reviewed Fuhrman nuclear grading in a series of 388 conventional RCCs.[28] Concordance was moderate with original grade 1 tumors up shifted by 1 grade in 38.7% of cases, by 2 in 18.9% and by 3 in 2.7% ($\kappa = 0.44$). The original grade 2 tumors were upgraded by 1 grade in 34% of cases and by 2 grades in 4.3%. Original grades 3 and 4 remained unchanged in 73.1% and 89.3% of cases, respectively.

Al-Aynati et al assessed the intra-observer reproducibility of the Fuhrman grading system among 4 experienced pathologists, who graded 99 RCCs on 2 occasions with a minimum of 3 months separating the 2 readings.[42] Intra-observer κ was 0.29 to 0.62 (mean 0.45), indicating moderate agreement. After combining Fuhrman grades 1 and 2 as low grade and grades 3 and 4 as high grade, intra-observer κ was 0.4 to 0.64 (mean 0.53), showing substantial agreement after grade clustering. Table 4 shows series assessing the inter-observer and intra-observer reproducibility of the Fuhrman grading system for RCC.[2,9,17,38,42,43]

2) The variability of cancer specific survival probabilities stratified by grade could depend on the heterogeneity of RCC, which often presents as areas with different grades in the same tumor.[32] Al-Aynati reported more than 1 grade even in 53% of cases with heterogeneity the rule more than the exception.[42] Hence, some pathologists would upgrade a grade 2 tumor according to a small focus of higher grade nuclei detected at high power, while others would resist this. Although nuclear grade should be based on the worst identified area, there is still a lack of consensus about the minimal size to be considered significant.[11,31,42] The Mayo Clinic group proposed recording the highest grade that occupies at least 1 high power field.[21,25]

3) Suboptimal tissue fixation, different fixation solution and fixation protocols can markedly affect nuclear grading attribution. After suboptimal fixation Goldstein reported nucleoli disappearance and chromatin modification being coarser and less hyperchromatic, which might cause grade migration.[11,32]

An additional explanation of the variability of reported cancer specific survival probabilities is histotype. Although the UICC and American Joint Committee on Cancer recommended assigning nuclear grades only for conventional and papillary RCC,[31] most groups have presented data on series including all histological subtypes of RCC without stratification. In a large series from the Mayo Clinic Cheville et al recently underlined the survival difference among different histotypes.[25] When stratifying by histological subtypes and nuclear grades, overlapping survival probabilities were observed between grades 1 and 2 tumors regardless of tumor histological subtype. Similarly patients with grade 3 conventional RCC had a worse outcome than those with grade 3 papillary and chromophobe RCC, while the prognosis was poor for grade 4 RCC of any histological subtype.

With the intent to improve the prognostic accuracy of nuclear grade nuclear morphometry was developed. With computer imaging technology image based morphometry aims to quantitatively assess nuclear descriptor factors, such as nuclear diameter, nuclear perimeter, nuclear area, the roundness factor and nucleolar area.[44–46] Although a few studies have the prognostic relevance of nuclear morphometry, this methodology has not gained wide diffusion.

TABLE 4. *RCC grading system interobserver and intra-observer reproducibility*

References (grading system)	No. Pts	Histological Subtype	No. Grades	No. Pathologists	Agreement	Reproducibility
Lanigan et al:[2]	88	Any		4	Interobserver	Moderate
Arner			3			$\kappa = 0.24$
Skinner			4			$\kappa = 0.26$
Syrjanen-Hjet			4			$\kappa = 0.42$
Fuhrman			4			$\kappa = 0.33$
Bretheau et al (Fuhrman)[17]	190	Any	4	2	Interobserver	High (concordance 95%)*
Lohse et al (Mayo Clinic standardized)[9]	1,733	Clear cell RCC	4	30 (original diagnosis), 1 (revision)	Interobserver	Higher reported Ca specific survival predictability for standardized grading system
Al-Aynati et al (Fuhrman)[42]	99		4, 2 (G1–2 vs 3–4)	4, 4	Interobserver	Moderate ($\kappa = 0.29, 0.45$)
Al-Aynati et al (Fuhrman)[42]	99		4, 2 (G1–2 vs 3–4)	4, 4	Intra-observer	Moderate ($\kappa = 0.45$, substantial ($\kappa = 0.53$)
Ficarra et al (Fuhrman)[38]	38	Clear cell RCC	4	5 (original diagnosis), 1 (revision)	Interobserver	Moderate ($\kappa = 0.44$)
Lang et al (Fuhrman)[43]	241	Any	4, 3, 2	3	Interobserver	Moderate ($\kappa = 0.22, 0.29–0.34, 0.44$)

The κ statistic is a measure of agreement between observers that corrects for chance agreement with degree of concordance defined as fair— $\kappa = 0.00$ to 0.20, moderate— $\kappa = 0.46$ to 0.75 and almost perfect— $\kappa = 0.76$ to 0.99.[41]
* No correction for chance agreement.

CONCLUSIONS

Many years have passed since the famous statement of Skinner et al, who wrote that "it is easier to invent one's own classification than to abide by another's."[4] Nuclear grade is better studied than other histological systems and it is the most widespread. Several series demonstrate its independent prognostic value.

According to the 1997 Rochester Workshop the 3-grade system is currently recommended.[31] Although few large, multicenter studies have demonstrated statistically significant survival differences between patients with grades 1 and 2 tumors, and a detrimental loss of statistical accuracy after grade clustering,[47] the clinical relevance of such statistical significance remains to be better elucidated.

Due its important prognostic role grading systems should be included in all prognostic algorithms and nomograms predicting disease-free and cancer specific survival probabilities. However, there is still a need for better standardization of fixation protocols, nuclear criteria and minimal size of the worst area to be considered significant for grading tumors to improve the reproducibility of grading system. A major consensus should be achieved by uropathologists. Especially in old retrospective series slide review and grade reassignment must be regarded as the gold standard for further prognostic studies of nuclear grade. Almost 10 years after the Rochester Workshop a further consultation is needed to speed this processes.

Abbreviations and Acronyms

ECOG = Eastern Cooperative Oncology Group
PS = performance status
RCC = renal cell carcinoma
SSIGN = Stage, Size, Grade and Necrosis

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C et al: Cancer statistics 2006. CA Cancer J Clin 2006; **56:** 106.
2. Lanigan D, Conroy R, Barry-Walsh C, Loftus B, Royston D and Leader M: A comparative analysis of grading system in renal adenocarcinoma. Histopathology 1994; **24:** 473.
3. Arner O, Blanck C and von Schreeb T: Renal Adenocarcinoma; morphology—grading of malignancy—prognosis. A study of 197 cases. Acta Chir Scand 1965; suppl **346:** 1.
4. Skinner DG, Colvin RB, Vermillion CD, Pfister RC and Leadbetter WF: Diagnosis and management of renal cell carcinoma. A clinical and pathological study of 309 cases. Cancer 1971; **28:** 1165.
5. Syrjanen K and Hjelt L: Grading of human renal adenocarcinoma. Scand J Urol Nephrol 1978; **12:** 49.
6. Fuhrman SA, Lasky LC and Limas C: Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982; **6:** 655.
7. Thoenes W, Storkel S and Rumpelt HJ: Histopathology and classification of renal cell tumors (adenomas, oncocytomas, and carcinomas). The basic cytological and histopathological elements and their use for diagnostics. Pathol Res Pract 1986; **181:** 125.
8. Delahunt B and Nacey JN: Renal cell carcinoma. II. Histological indicators of prognosis. Pathology 1987; **19:** 258.
9. Lohse CM, Blute ML, Zincke H, Weaver AL and Cheville JC: Comparison of standardized and nonstandardized nuclear grade of renal cell carcinoma to predict outcome among 2,042 patients. Am J Clin Pathol 2002; **118:** 877.
10. Hand JR and Broders A: Carcinoma of the kidney: the degree of malignancy in relation to factors bearing on prognosis. J Urol 1931; **28:** 199.
11. Goldstein NS: Grading of renal cell carcinoma. Urol Clin North Am; 1999; **26:** 637.
12. Medeiros LJ, Gelb AB and Weiss LM: Renal cell carcinoma: prognostic significance of morphologic parameters in 121 cases. Cancer 1988; **61:** 1639.
13. Grignon DJ, Ayala AG, el-Naggar A, Wishnow KI, Ro JY, Swanson DA et al: Renal cell carcinoma. A clinicopathologic and DNA flow cytometric analysis of 103 cases. Cancer 1989; **64:** 2133.
14. Green LK, Ayala AG, Ro JY, Swanson DA, Grignon DJ, Giacco GG et al: Role of nuclear grading in stage I renal cell carcinoma. Urology 1989; **34:** 310.
15. Munichor M, Lichtig C, Tzin G and Weiss A: Prognostic significance of granular cell content in renal cell carcinoma. Eur Urol 1992; **22:** 204.

16. Gelb AB, Shibuya RB, Weiss LM and Medeiros LJ: Stage I renal cell carcinoma. A clinicopathologic study of 82 cases. Am J Surg Pathol 1993; **17:** 275.
17. Bretheau D, Lechevalier E, De Fromont M, Sault MC, Rampal M and Coulange C: Prognostic value of nuclear grade of renal cell carcinoma. Cancer 1995; **76:** 2543.
18. Usubutun A, Uygur MC, Ayhan A, Toklu C, Sahin A, Ozen H et al: Comparison of grading systems for estimating the prognosis of renal cell carcinoma. Int Urol Nephrol 1998; **30:** 391.
19. Tsui KH, Shvarts O, Smith RB, Figlin RA, de Kernion JB and Belldegrun A: Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. J Urol 2000; **163:** 1090.
20. Ficarra V, Righetti R, Martignoni G, D'Amico A, Pilloni S, Rubilotta E et al: Prognostic value of renal cell carcinoma nuclear grading: multivariate analysis of 333 cases. Urol Int 2001; **67:** 130.
21. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL and Zincke H: 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.
22. Minervini A, Lilas L, Minervini R and Selli C: Prognostic value of nuclear grading in patients with intracapsular (pT1-pT2) renal cell carcinoma. Long-term analysis in 213 patients. Cancer 2002; **94:** 2590.
23. Amin MB, Amin MB, Tamboli P, Javidan J, Stricker H, de-Peralta Venturina M et al: Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: experience of 405 cases. Am J Surg Pathol 2002; **26:** 281.
24. Ficarra V, Prayer-Galetti T, Novella G, Bratti E, Maffei N, Dal Bianco M et al: Incidental detection beyond pathological factors as prognostic predictor of renal cell carcinoma. Eur Urol 2003; **43:** 663.
25. Cheville JC, Lohse CM, Zincke H, Weaver AL and Blute M: Comparison of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 2003; **27:** 612.
26. Mejean A, Hopirtean V, Bazin JP, Larousserie F, Benoit H, Chretien Y 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.
27. Erdogan F, Demirel A and Polat O: Prognostic significance of morphologic parameters in renal cell carcinoma. Int J Clin Pract 2004; **58:** 333.
28. Ficarra V, Martignoni G, Maffei N, Brunelli M, Novara G, Zanolla L 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.
29. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A et al: Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005; **23:** 2763.
30. Gudbjartsson T, Thoroddsen A, Petursdottir V, Hardarson S, Magnusson J and Einarsson GV: Effect of incidental detection for survival of patients with renal cell carcinoma: results of population-based study of 701 patients. Urology; 2005; **66:** 1186.
31. Medeiros LJ, Jones EC, Aizawa S, Aldape HC, Cheville JC, Goldstein NS et al: Grading of renal cell carcinoma: workgroup No. 2. Union Internationale Contre le Cancer and the American Joint Committee on Cancer (AJCC). Cancer 1997; **80:** 990.
32. Goldstein NS: The current state of renal cell carcinoma grading. Union Internationale Contre le Cancer and the American Joint Committee on Cancer (AJCC). Cancer 1997; **80:** 977.
33. Zisman A, Pantuck AJ, Dorey F, Said JW, Shvarts O, Quintana D et al: Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001; **19:** 1649.
34. Zisman A, Pantuck AJ, Wieder J, Chao DH, Dorey F, Said JW et al: Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002; **20:** 4559.
35. Han KR, Bleumer I, Pantuck AJ, Kim HL, Dorey FJ, Janzen NK et al: Validation of an integrated staging system toward improved prognostication of patients with localized renal cell carcinoma in an international population. J Urol 2003; **170:** 2221.
36. Patard JJ, Kim HL, Lam JS, Dorey FJ, Pantuck AJ, Zisman A et al: Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 2004; **22:** 3316.
37. Bretheau D, Lechevall E, Eghazarian C, Grisoni V and Coulange C: Prognostic significance of incidental renal cell carcinoma. Eur Urol 1995; **27:** 319.
38. Ficarra V, Martignoni G, Lohse C, Novara G, Pea M, Cavalleri S 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.
39. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Leibovich BC et al: A multifactorial postoperative surveillance model for patients with surgically treated clear cell renal cell carcinoma. J Urol 2003; **170:** 2225.
40. Sorbellini M, Kattan MW, Snyder ME, Reuter V, Motzer R, Goetzl M et al: A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol 2005; **173:** 48.
41. Munoz S and Bangdiwala S: Interpretation of Kappa and B statistics measures of agreement. J Appl Stat 1997; **24:** 105.
42. Al-Aynati M, Chen V, Salama S, Shuhaibar H, Treleaven D and Vincic L: Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. Arch Pathol Lab Med 2003; **127:** 593.
43. Lang H, Lindner V, de Fromont M, Molinie V, Letourneux H, Meyer N et al: Multicenter determination of optimal interobserver agreement using the Fuhrman grading system for renal cell carcinoma: assessment of 241 patients with >15-year follow-up. Cancer 2005; **103:** 625.
44. Carducci MA, Piantadosi S, Pound CR, Epstein JI, Simons JW, Marshall F et al: Nuclear morphometry adds significant prognostic information to stage and grade for renal cell carcinoma. Urology 1999; **53:** 44.
45. Montironi R, Santinelli A, Pomante R, Mazzucchelli R, Colanzi P, Longatto Filho A et al: Morphometric index of adult renal cell carcinoma. Comparison with the Fuhrman grading system. Virchows Arch 2000; **437:** 82.
46. Ozer E, Yorukoglu K, Sagol O, Mungan U, Demirel D, Tuzel E et al: Prognostic significance of nuclear morphometry in renal cell carcinoma. BJU Int 2002; **90:** 20.
47. Rioux-Leclercq N, Leray E, Fergelot P, Mejean A, Valeri A, Ficarra V et al: The nuclear Fuhrman grade: a European multicentre study for the determination of the optimal grading system in term of prognosis. Eur Urol, suppl., 2006; **5:** 67.