Simplification of the Fuhrman grading system for renal cell carcinoma

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Introduction: *The Fuhrman grading system (FGS) is the most widely utilized pathological classification and predictor of renal cell carcinoma (RCC) prognosis. The aim of this study was to test the prognostic ability of a simplified two-tier FGS.*

Materials and methods: *We reviewed the data of 509 patients with clear cell RCC who underwent radical or partial nephrectomy between January 1994 and April 2007. The conventional four-tier (I, II, III, IV) FGS was compared to a simplified two-tier FGS in which grades I and II were combined (low grade) and grades III and IV were combined (high grade). Cancer-specific survival (CSS) was calculated for each patient. Univariate and multivariate analyses were used in combination with area under the curve (AUC) of receiver operating characteristic curves to compare prognostic accuracies between grading schemes.*

Results: *Median follow up was 81.6 months. Using the conventional FGS, the 5 year CSS for Fuhrman grades I, II, III, and IV were 74.1%, 76.0%, 57.3%, and 40.7%, respectively ($p < 0.001$). Using the simplified two-tier FGS, the 5 year CSS for low grade and high grade were 75.5% and 54.7%, respectively ($p < 0.001$). Both FGSs achieved independent predictor status in multivariate analyses. Prognostic accuracy of multivariate models between the two FGSs had nearly identical AUCs, with a c-statistic of 0.769 and 0.716 for the two-tier and conventional systems, respectively.*

Conclusions: *Our findings indicate that the simplified FGS performs similarly to the conventional system. The use of this simplified system may promote greater continuity of pathological interpretation as well as provide a more simplified approach for clinician utilization.*

Key Words: kidney cancer, carcinoma, renal cell, nephrectomy, prognosis, pathology, surgical

Introduction

The Fuhrman grading system (FGS) is the most widely utilized pathological classification of renal cell carcinoma (RCC). Introduced in 1982, the FGS is based on assessment of the cell nucleus, assigning a grade based on uniformity of nuclear size, nuclear shape, and nucleolar prominence.[1] The FGS in itself has proven to be an independent predictor of survival and metastatic potential.[1,2] The conventional FGS categorizes RCC specimens into grades I, II, III, or IV. In recent years, however, simplified FGSs have been validated.[3-6] The aim of this study was to test the fidelity and prognostic ability of a simplified two-tier (low grade and high grade) FGS against our institutional cohort of patients who received surgical treatment for RCC.

Materials and methods

Upon institutional review board approval, we reviewed the data of 961 patients who underwent radical or partial nephrectomy between January 1994 and April 2007. Clear cell RCC was the histologic subtype in 509 patients. Due to the relative lack of validation of the FGS in other subtypes of RCC, we chose to limit our analysis to the clear cell variant.[7,8] Clinical and pathologic data were reviewed for each case. This included all pertinent follow up evaluations with thorough review of any clinical, laboratory, and radiological outcomes.

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Tumors were staged according to the 2010 Tumor-Node-Metastasis (TNM) staging system.[9] Tumor size was measured on pathological analysis and was defined as the greatest diameter on sectioning. All surgical specimens were examined by dedicated genitourinary pathologists immediately following surgery.

The conventional four-tier FGS was compared to a simplified two-tier FGS in which grades I and II were combined (low grade) and grades III and IV were combined (high grade). Survival was calculated from the time of surgery to the time of last follow up. Non-RCC related deaths were excluded from analysis. Kaplan-Meier method was used to graphically depict survival curves. Log-rank test was used for survival comparison between Fuhrman grades. Univariate analyses were performed with Pearson's chi-squared and Fisher's exact tests for categorical variables and ANOVA and Student's t-test for continuous variables. Multivariate analyses were performed with logistic regression for two-tier FGS and multinomial logistic regression for the conventional FGS. Prognostic accuracy of multivariate models between the two FGSs were quantified using the area under the curve (AUC) of receiver operating characteristic curves. All tests were two-sided with statistical significance set at $p \leq 0.05$. All statistical tests were performed with Stata Statistical Software: Release 13 (StataCorp, College Station, TX USA).

Results

Characteristics of all 509 patients are presented in Table 1. Median age of the population was 60.2 years (range 23-90). Seventy (14%), 198 (39%), 133 (26%), and 108 (21%) patients had a renal mass of < 2 cm, 2.1 cm-4 cm, 4.1 cm-7 cm and > 7 cm, respectively. Median follow up was 81.6 months (range 0.1-163.1). Fuhrman grade was only available for 441 patients due to non-definitive grading in 68 patients. All Fuhrman analyses were limited to these patients. The number of patients with Fuhrman grades I, II, III, and IV were 54 (12%), 266 (60%), 102 (23%), and 19 (4%), respectively.

Mean recurrence time for all patients in the series was 22.8 months (IQR 6.1-37.0). Using the two-tier FGS, low grade and high grade tumors had a mean time to recurrence of 24.7 and 6.29 months ($p = 0.01$) and a mean time to death of 43.2 and 20.1 months ($p = 0.002$), respectively, Table 2. The 2 year, 5 year, and 10 year cancer-specific survivals (CSS) for the entire cohort (independent of Fuhrman grade) were 79.5%, 68.1%, and 64.9%, Figure 1a. Using the conventional FGS, the 5 year CSS for Fuhrman grades I, II, III, and IV were 74.1%, 76.0%, 57.3%, and 40.7%, respectively ($p < 0.001$), Figure 1b. Using the simplified two-tier FGS, the 5 year CSS for low grade and high grade were 75.5% and 54.7%, respectively ($p < 0.001$) Figure 1c. Figure 1d displays the CSS of the conventional and simplified FGS superimposed upon each other for comparison.

Both FGSs achieved independent predictor status in multivariate analyses. Prognostic accuracy of multivariate models between the two FGSs had nearly identical AUCs, with a c-statistic of 0.769 and 0.716 for the two-tier and conventional systems, respectively, Table 3.

TABLE 1. **Patient characteristics**

	Patients, n (%)
Age (years)	
≤ 49	108 (22)
50-59	128 (26)
60-69	130 (27)
70-79	110 (22)
≥ 80	17 (3)
Sex	
Male	318 (62)
Female	191 (38)
Race	
Caucasian	373 (73)
Black	53 (11)
Other	83 (16)
Smoking history	
No	196 (42)
Yes	271 (58)
VHL status	
No	158 (93)
Yes	12 (7)
Resection type	
Radical	147 (29)
Partial	362 (71)
Side	
Left	280 (55)
Right	227 (45)
Bilateral	2 (< 1)
Fuhrman grade	
I	54 (12)
II	266 (60)
III	102 (23)
IV	19 (4)

TABLE 2. **Survival and recurrence data**

	Low grade	High grade	p value
Status, n (%)			**< 0.0001**
Alive	277 (62)	84 (19)	
Dead	49 (11)	39 (8)	
First recurrence, n (%)			**< 0.0001**
None	313 (69)	106 (23)	
< 12 months	5 (1)	13 (3)	
12-36 months	6 (1)	2 (< 1)	
36-60 months	3 (< 1)	3 (< 1)	
> 60 months	4 (< 1)	0 (0)	
Mean time to recurrence (months)	24.7	6.29	**0.01**
Mean time to death (months)	43.2	20.1	**0.002**

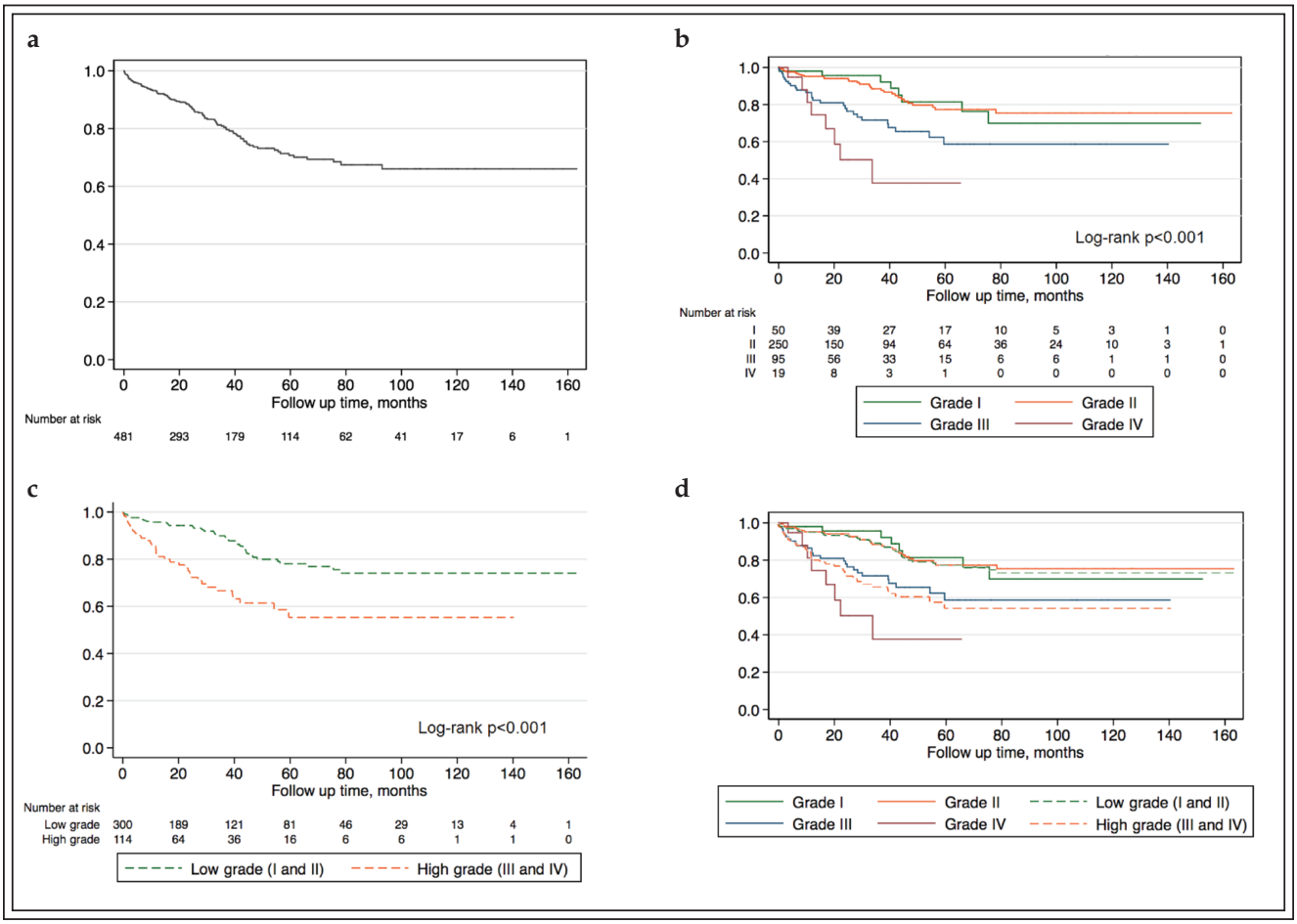

Figure 1a. Kaplan-Meier plots showing the cancer-specific survival of patients. **(a)** All patients in the analysis, independent of Fuhrman grade. **(b)** Stratified by the conventional, four-tier Fuhrman grading system. **(c)** Stratified by the simplified, two-tier Fuhrman grading system. **(d)** Conventional and simplified Fuhrman grading systems superimposed upon each other for comparison.

TABLE 3. **Comparison of Fuhrman grading systems**

	Traditional (I vs. II vs. III vs. IV) OR	95% CI	Two-tier (low, I-II vs. high, III-IV) OR	95% CI
Age				
50-59 vs. ≤ 49	0.824	0.451-1.506	1.044	0.508-2.147
60-69 vs. ≤ 49	0.986	0.538-1.808	0.964	0.471-1.974
70-79 vs. ≤ 49	1.161	0.618-2.180	0.756	0.357-1.603
≥ 80 vs. ≤ 49	1.661	0.530-5.205	0.263	0.050-1.390
Sex				
Male vs. female	1.314	0.864-2.000	0.687	0.413-1.143
Tumor stage				
T2 vs. T1	0.625	0.234-1.666	1.304	0.444-3.832
T3a vs. T1	0.332	0.162-0.681	2.727	1.250-5.949
T3b vs. T1	0.267	0.124-0.578	3.476	1.499-8.063
T3c vs. T1	> 999.9	< 0.001-> 999.9	< 0.001	< 0.001-> 999.9
Tumor size				
< 2.0 vs. > 7.0	3.979	1.448-10.932	0.203	0.061-0.679
2.1-4.0 vs. > 7.0	2.957	1.253-6.980	0.209	0.080-0.543
4.1-7.0 vs. > 7.0	1.625	0.717-3.680	0.577	0.232-1.431
First recurrence				
< 12 months vs. none	0.286	0.108-0.754	3.442	1.049-11.289
12-36 months vs. none	1.523	0.370-6.265	0.330	0.059-1.861
36-60 months vs. none	0.995	0.174-5.687	1.174	0.170-8.102
> 60 months vs. none	3.469	0.431-27.884	< 0.001	< 0.001-> 999.9

Discussion

In 2015, renal malignancies accounted for an estimated 61,560 new cancer diagnoses and 14,080 deaths in the United States.[10] The FGS is widely used to characterize these patients into appropriate risk groups, contributing to proper prognostication. Unfortunately, a low level of interobserver agreement has limited the interpretation of these four grades, adding an unnecessary complexity to their application.[11-15] Considering this shortcoming of the traditional FGS, we sought to compare this to a simplified system using our institutional database of surgically managed RCC patients as a reference population.

The first published proposal of a simplified FGS was by Zisman et al in 2001, where the authors suggested a two-tier system by combining grades I and II and grades III and IV together, as done in the present study.[13] Shortly after, Ficarra et al proposed a three-tier system by combining grades I and II and leaving grades III and IV unchanged.[14] In recent years, the performance of both of these simplified FGSs have been evaluated by multiple authors.[3,4,6]

Of the numerous validations of simplified FGSs, two are of note due to the size of their study cohort. The largest analysis comes from Sun et al, who analyzed 14,064 patients from the Surveillance, Epidemiology, and End Results (SEER) cancer registries in the United States.[4] The second largest is from Rioux-Leclercq et al, who evaluated a cohort of 5453 patients from multiple high-volume European centers.[3] Each of these studies tested the conventional four-tier FGS against both two- and three-tier systems. It was concluded by both groups that each simplified FGS performed without loss of prognostic accuracy regarding survival after partial or radical nephrectomy. Importantly, the European study analyzed all subtypes of RCC while the American study analyzed only the clear cell variant.

Given the relative equality of both revised FGSs, we chose to analyze a two-tier system as opposed to a three-tier in order to provide as much simplification as possible without compromising its usefulness and fidelity. Furthermore, Fuhrman et al disclosed in their initial publication that grades I and II are distinguished from grades III and IV in an easier fashion than any

further separation of grading.[1] This is secondary to a much lower requirement of magnification to differentiate between the two lowest and the two highest grades than to perform further sub-stratification.

Analogous to the results of these other studies,[3,4,6,14] we found that the two-tier FGS performs similarly to the conventional four-tier system. Both systems accurately predicted survival and recurrence outcomes similarly while both achieving independent predictor status on multivariate analysis.

A similar binary system was introduced for urothelial carcinoma in 2004 by the World Health Organization (WHO) and International Society of Urological Pathology (ISUP). This system classifies lesions as either low grade or high grade (while also reserving a nonmalignant classification for lesions of low malignant potential). This way of grading has proven to maintain prognostic significance while simplifying the previously used system.[16,17] It is the feeling of the authors that the widespread acceptance of the WHO/ISUP 2004 classification leaves little question that a simplified FGS would be quickly adopted. However, militia mentality should not dictate clinical practice, and as pointed out by Ficarra et al, it would be prudent to have a multidisciplinary expert consensus before standardizing the implementation of any new grading system for RCC.[18]

Given the above presented issues, the ISUP convened a consensus conference in 2012 to produce guidelines and recommendations regarding the RCC staging, classification, and grading.[19,20] Unfortunately, the "Vancouver Classification of Renal Neoplasia" as it is titled, has yet to gain popularity in use. Therefore, the standard of care has remained the previous classification system, which includes the FGS.

Conclusions

Our findings indicate that this simplified two-tier FGS performs similarly to the conventional system in prognosticating patients with clear cell RCC. The use of a simplified system may promote greater continuity of pathological interpretation as well as provide a more simplified approach for clinician utilization without affecting the function for which it was intended. Given the growing body of evidence supporting simplified FGSs, a multidisciplinary expert consensus would be beneficial to facilitate appropriate adoption. □

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