Original Article

Application and comparison of Fuhrman nuclear grading system with the novel tumor grading system for chromophobe renal cell carcinoma and its correlation with disease-specific events

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ABSTRACT

Introduction: The grading system of chromophobe renal cell carcinoma (ChRCC) is not well established. In this study, we aimed to compare the application of Fuhrman nuclear grade (FNG) with the novel chromophobe tumor grade (CTG). We also evaluated the correlation of these two grading systems with the clinical outcome.

Materials and Methods: Consecutive cases of ChRCC diagnosed on nephrectomy during 2005–2014 were identified. The clinical details of the patients were retrieved. Histopathology slides were reviewed and the nuclear grading was assigned using standard FNG and the CTG system. The CTG and FNG gradings were correlated with clinical outcome.

Results: A total of 80 cases were retrieved. Distribution of FNG was as follows: FNG-1, 1 (1.3%); FNG-2, 23 (28.3%); FNG-3, 44 (55.0%); and FNG-4, 12 (15%). CTG distribution was as follows: CTG-1, 48 (60.0%); CTG-2, 20 (25.0%); and CTG-3 12 (15.0%). Follow-up data was available in 46 cases; the median follow-up was 23.9 months (range 1–96.4 months). The median time to recurrence/metastasis was 17.2 months (range 3.2–31.2 months). Mean disease-free survival (DFS) was 68.5 months. Both CTG ($P < 0.001$) and FNG ($P = 0.001$) correlated with DFS; however, only CTG retained this significance when only the nonsarcomatous cases were analyzed. On receiver operating characteristics curve analysis, CTG had higher predictive accuracy for DFS for the entire group, while FNG lost the statistical significance when the nonsarcomatous cases were analyzed. CTG ($P = 0.001$) but not FNG ($P = 0.106$) correlated with the disease-specific adverse events in non-sarcomatous cases.

Conclusions: It is possible to apply CTG in ChRCC. It is a better predictor of DFS and disease-specific adverse events. CTG is more appropriate and applicable than the FNG in grading ChRCC.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 2.2% of cases of the global cancer burden and about 1.8% of cases of global cancer-related mortality.[1] It is estimated that RCC will account for approximately 2% overall cancer burden amongst Indian males.[2] The common histologies encountered by a pathologist in RCC are the conventional clear cell RCC, papillary RCC, and chromophobe RCC (ChRCC). Although stage remains the most powerful prognosticator dictating the outcome, in smaller tumors,

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the nuclear grade may aid in directing management and the follow-up or surveillance schedule (frequency of follow-up/abdominal contrast-enhanced computed tomography).[3,4] Fuhrman nuclear grade (FNG) was the most widely used grading system for RCC until recently when the International Society for Urological Pathology (ISUP) proposed a new grading system.[5] Some studies have even validated the clinical predictive value of FNG in RCC.[6] Hence, the grading of RCC does have a prognostic significance and may aid in appropriate clinical management decisions.[7-9] However, the usage of FNG is fraught with technical issues and cumbersome calculations of nuclear size, shape, and nucleoli, and hence, its utility in daily practice is limited to an assessment of nucleoli in practicality. The nuclear abnormalities of ChRCC nuclei are inherent to this tumor and hence, the applicability of FNG in ChRCC is controversial and may be inappropriate.[10-13] Moreover, these two types of RCC have drastically different prognoses with 10-year survival for ChRCC ranging from 80% to 90% in contrast to clear cell RCC which ranges from 45% to 70%.[12] To improve the grading of ChRCC, Paner *et al*. proposed an alternate grading system in the year 2010.[12] Since then, various attempts have been made to validate this system.[14-19] We undertook this study to evaluate the applicability and feasibility of this novel tumor grading system and compare it with the FNG system, as also with the disease-specific events.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee (IEC Project no 1570). Retrospective analysis of consecutively diagnosed cases of ChRCC over 10 years (2005–2014) was done. Diagnosed cases of ChRCC on nephrectomy/partial nephrectomy specimens were included while the cases diagnosed on biopsy samples were excluded. Clinical and pathologic data evaluated were: Age, sex, and tumor size. The histopathology slides of ChRCC were retrieved and reviewed by two pathologists (SM and GKB). One of the reviewers (SM), a full-time dedicated genitourinary pathologist, was blinded to the clinical outcome and the status of nodal/distant metastasis. The important histopathological parameters examined were sarcomatous differentiation and necrosis. The tumor in each case was assigned an FNG as well as the novel chromophobe tumor grade (CTG)[12] [Table 1]. The pathological staging was assigned based on the AJCC 7th edition cancer staging manual. The follow-up data were obtained from clinical case records and electronic medical records. Correlation of the FNG and novel CTG system was done with pathological parameters and disease-free survival (DFS). The data were analyzed using SPSS software version 20.0 (IBM, Armonk, NY, USA). For assessing the association of various pathological variables, the Chi-square test, Fischer's exact test, and Pearson's correlation coefficient test were used. Survival curves were calculated using the Kaplan–Meier method. Comparisons between curves were performed using the Mantel-Cox (log-rank) test. Both the grading systems were compared using receiver operating characteristics (ROC) curves. The area under the curve (AUC) and the 95% confidence intervals were noted. All the tests were applied at a 5% significance level.

RESULTS

A total of 86 cases reported as ChRCC on nephrectomy specimens were retrieved. Out of these 86 cases, five cases were reclassified as clear cell RCC based on morphological and immunohistochemical findings and hence were excluded from the study cohort. One case with only slides from a recurrent ChRCC tumor was also excluded. The remaining cohort of 80 cases included both, the in-house operated (n = 31; 38.8%), and referral cases (n = 49; 62.2%). Seventy-three cases (91.3%) had undergone radical nephrectomy and four cases (5%) had partial nephrectomy specimens. Surgical details were not available in three cases (3.8%). The major clinicopathological variables are summarized in Supplementary Table 1. The median age was 52 years (range 27–77 years). Forty-four (55%) patients were male and 36 (45%) were female (M:F = 1.2:1). The mean tumor size was 10.38 cm (range 3 cm to 28 cm). Microscopically, necrosis was seen in 21 cases (26.3%) and sarcomatous differentiation was noted in nine cases (11.3%).

Grading of ChRCC with FNG and CTG

FNG had been assigned in 31 cases during initial reporting. Out of 22 cases initially graded as FNG-2, eight cases were re-assigned to FNG-3, one case was re-assigned as FNG-4, and 13 cases were confirmed as FNG-2. Out of seven cases initially reported as FNG-3, one case each was reassigned as FNG-2 and FNG-4, and the rest were retained as FNG-3. One case each initially graded as FNG-1 and FNG-4 were confirmed at the review. Hence, the distribution of FNG in the present cohort (80 cases) was as follow: FNG-1 (n = 1; 1.3%), FNG-2 (n = 23; 28.3%), FNG-3 (n = 44; 55.0%), and FNG-4 (n = 12; 15.0%). On applying CTG to the tumors, 48 cases (60.0%) were CTG-1, 20 cases (25.0%) were CTG-2, and 12 cases (15.0%) were CTG-3 [Figure 1]. CTG-3 cases included nine cases (11.3%) harboring sarcomatous differentiation. When FNG was compared with CTG, FNG-1 and FNG-4 corresponded to CTG-1 and CTG-3, respectively. All 23 cases of FNG-2 were assigned CTG-1. Of the 44 cases assigned FNG-3, 24 cases were downgraded to CTG-1, and 20 cases were placed in CTG-2 [Figure 2].

Staging (including pT stage, nodal status)

pT stage could be assigned in 51 cases; the distribution being as follows: pT1 (n = 15, 29.4%), pT2 (n = 13; 25.5%), and pT3 (n = 23; 44.4%). Upfront regional lymph node dissection was done in 40 cases, of which three cases (3.8%) showed nodal metastasis. Overall a complete TNM staging was possible in 38 cases. Twelve cases (31.6%) were stage

Table 1: Comparison of Fuhrman nuclear grading system and Chromophobe tumor grading system

Grades	Fuhrman Nuclear Grade			Chromophobe Tumor Grades	
	Nuclear diameter (in micrometer)	Nuclear shape	Nucleoli	Nuclear Crowding	Nuclear Anaplasia
Grade 1	10	Round/ uniform	Absent/ inconspicuous	Absent	Absent (Usual wide constitutive nuclear range)
Grade 2	15	Irregular outline	Visible at 400x magnification	Geographic crowding (cellular clustering characterized by high nuclear/cytoplasmic density when viewed at 100x, nuclei touching each other when viewed at 400x)	Nuclear pleomorphism >3 fold variation and distinct chromatin irregularities
Grade 3	20	Obviously irregular outline	Visible/ prominent at 100x	Absent/Present	Frank anaplasia (polylobation, giant cells) or sarcomatous change
Grade 4	Marked nuclear pleomorphism			-	

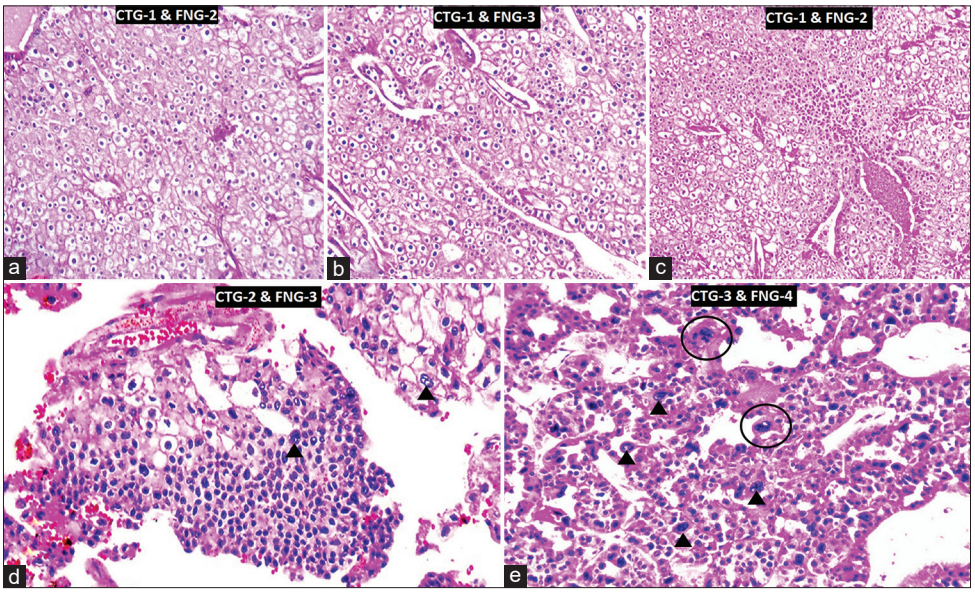

Figure 1: (a) Constitutive nuclear range without nuclear crowding and anaplasia; (b) nucleomegaly without nuclear crowding; (c) nuclear crowding without nuclear pleomorphism ≥3-fold; (d) nuclear crowding, irregularity, and pleomorphism ≥3-fold (arrowheads); (e) nuclear anaplasia (arrowheads), polylobation, and tumor giant cells (circles). (a-c: ×100, d-f: ×400)

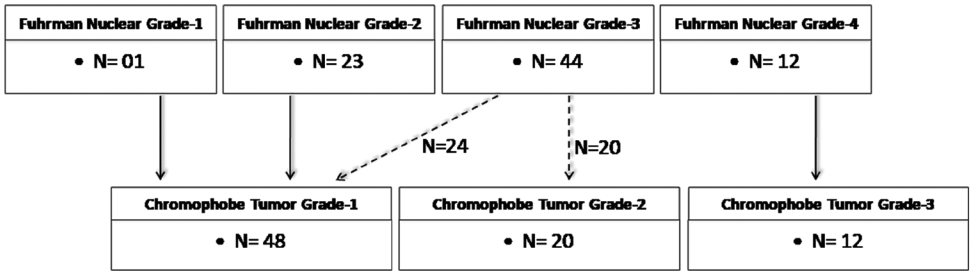

Figure 2: Number of cases as per Fuhrman nuclear grades and chromophobe tumor grades, and the redistribution of cases on a review when the tumors graded with Fuhrman nuclear grades were scored according to the chromophobe tumor grades

I, nine cases (23.7%) were stage II, 11 cases (28.9%) were stage III, and six cases (15.8%) were stage IV.

Follow-up

Follow-up was available in 46 cases. The median follow-up was 23.9 months (range 1–96.4 months). Five cases had metastasis at presentation (of which three cases had sarcomatous differentiation and two cases were nonsarcomatous). In addition, during follow-up, distant metastasis developed in 4 patients and local/locoregional recurrence occurred in three cases (two renal-bed recurrences and one paraaortic lymph node recurrence). The median time to recurrence/metastasis was 17.2 months (range 3.2 months to 31.2 months). The mean DFS for the whole group was 68.5 months. For analysis purpose, event time was taken as 1 month in the five cases which presented with metastasis (similar to Paner *et al.*).[12]

Correlation of grading system with DFS, recurrence, and metastasis

For the entire cohort, FNG and CTG had a statistically significant correlation with DFS ($P = 0.001$ and $P < 0.001$, respectively) [Supplementary Table 2 and Figure 3]. No event occurred in FNG-1 and FNG-2 tumors. The mean DFS of FNG-3 cases was 72.30 months and in FNG-4 cases it was 14.64 months. In contrast, no event occurred in CTG-1 tumors, whereas CTG-2 had a mean DFS of 44.51 months and CTG-3 had a mean DFS of 14.64 months. Univariate analysis, when applied only to nonsarcomatous cases, showed that CTG had a significant correlation with DFS ($P < 0.001$) in contrast to FNG ($P = 0.272$).

If only nonsarcomatous cases were taken into account, it was found that, as CTG increased there was a significant increase in the risk of disease-specific events (recurrence/metastasis) ($P = 0.001$) as against the FNG ($P = 0.106$). The ROC curve analysis was done for the whole cohort and nonsarcomatous cases separately. For the whole cohort, the AUC for CTG and FNG was 0.919 and 0.818, respectively, while for the nonsarcomatous cases the AUC for CTG and FNG was 0.903 and 0.724 respectively, [Supplementary Table 2].

DISCUSSION

The FNG was a widely used system for grading RCC including ChRCC until recently when Delahunt *et al*. questioned the utility of this grading system for ChRCC.[11] Attempts made by Lohse *et al*. to refine the FNG into a four-tier grading with an emphasis on nuclear prominence to suit ChRCC was not able to stratify the outcome in grades ≤3 tumors.[20] Later, Paner *et al*. proposed a novel grading system called CTG that did not take into account the nuclear characteristics (size and shape) of ChRCC.[12] There was a significant correlation between the CTG and the outcome.[12] This grading system was further validated in various studies conducted in different parts of the world.[14-19] Further, Cheville *et al*. established that although the CTG was associated with cancer-specific survival, it did not have an additional prognostic impact when the tumor stage and sarcomatous differentiation were evaluated.[15] We applied the CTG system to our cohort of patients and correlated it with disease-specific events.

The mean patient age (52.19 years) and the male-to-female ratio (1.2:1) in this study were comparable to earlier studies, wherein the mean age at presentation was 59 years.[21,22]

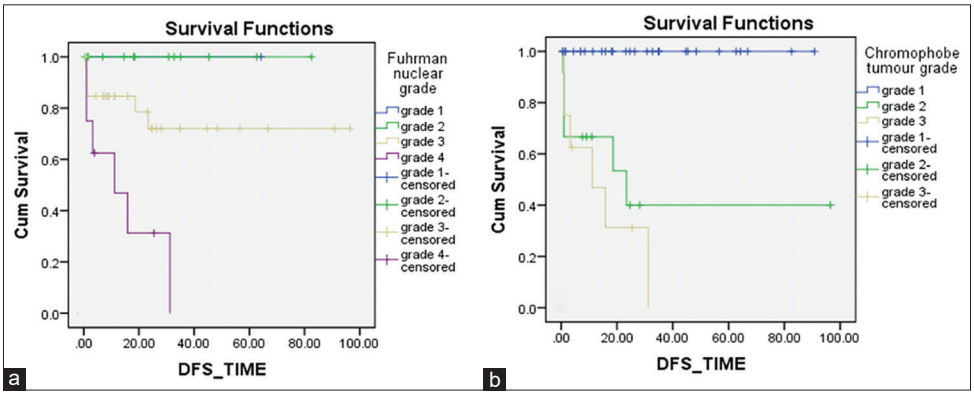

Figure 3: Kaplan–Meier plots for disease-free survival, (a) Fuhrman nuclear grade; (b) chromophobe tumor grade

Table 2: Comparison of chromophobe tumor grading (CTG) assigned to Chromophobe Renal Cell Carcinoma in different studies

Authors (reference)	Paner *et al*.[12]	Finley *et al*.[14]	Cheville *et al*.[15]	Sperga *et al*.[16]	Weinzierl *et al*.[17]	Xie *et al*.[18]	Lin *et al*.[19]	Present study
Year	2010	2011	2012	2013	2014	2017	2019	2020
Study Period	1968-2005 (38 years)	1992-2011 (20 years)	1970-2006 (37 years)	NA	1997-2010 (14 years)	2006-2015 (10 years)	2000-2017 (18 years)	2005-2014 (10 years)
No. of Cases	124	84	185	546	81	206	18	80
CTG 1	92 (74%)	40 (48.8%)	140 (75%)	252 (46.15%)	52 (64%)	142 (68%)	14 (78%)	48 (60%)
CTG 2	20 (16%)	30 (36.5%)	27 (15%)	177 (32.41%)	27 (34%)	54 (26%)	3 (17%)	20 (25%)
CTG 3	12 (10%)	12 (14.7%)	18 (10%)	84 (15.38%)	02 (2%)	13 (6%)	1 (6%)	12 (15%)
Follow-up (months: m, years: y)	Mean 48m, Median: 37m, Range: 1m to 182m	Median: 32.9m, Range: 0.37m to 138.2m	Mean: 10.5y, Median: 8.3y, Range 0-40y	NA	Mean: 53m, Range: 0.1m to 238m	Median: 48.4m, Range: 10.7m-129.9m	Median: 70.6m, Range: 3m to 205m	Median: 23.9m, Range: 1m to 96.4m
Outcome Recurrence (R), Metastases (M), Death due to disease (DOD)	R: 4 M: 15, DOD: 10	M: 11	M: 8, DOD: 23	NA	R: 2, M: 1, DOD: 1	R: 7, M: 6, DOD: 4	R: 0, M: 0, DOD: 1	R: 3, M: 4

The mean tumor size (10.38 cm) in this study, however, was larger as compared to those mentioned by Delahunt *et al*. (7.7 cm) and Amin *et al*. (8.0 cm).[11,21] The tendency of patients in our country to procrastinate seeking medical advice, due to logistical and financial constraints might be the reason for the larger tumor size at the presentation, in our series. The rate of necrosis (26.3%) and sarcomatous differentiation (11.25%) in our study is marginally more in comparison to Amin *et al*. (necrosis in 12.98% and sarcomatous differentiation in 8% cases).[21] Lower rates of sarcomatous differentiation in ChRCC have been reported by Cheville *et al*. (7% cases), and Przybycin *et al*. (2% cases).[13,15] The larger mean tumor size with a concomitant rise in chances of a sarcomatous differentiation and necrosis may be the reason for the slightly higher incidence of these aggressive histological features in our series.

Very few studies have evaluated FNG in ChRCC.[10-14] In most of these studies, the majority of ChRCC were assigned either FNG-2 or FNG-3 category. In our study, 44 cases (55%) were assigned FNG-3 on review of histopathology. Paner *et al*. placed as high as 74% of their ChRCC in the FNG-3 category in their series of 124 cases.[12] It is a well-established fact that ChRCC has lower malignant potential than conventional clear cell carcinoma and papillary RCC. Amin *et al*. in their study of 405 RCC cases found that clear cell carcinoma behaves aggressively than ChRCC.[23] Arguably then, FNG inevitably places ChRCC in higher grade owing to the inherent nuclear abnormalities seen in ChRCC. Thus, the FNG conveys a false overestimation of tumor nuclear grade to the treating genitourinary oncologists which may translate into unwarranted management and surveillance decisions. For the practicing pathologist, the application of FNG using the nuclear size in micrometer, shape, and nucleoli is cumbersome and fraught with variability. In comparison, applicability of CTG is based on geographical crowding and nuclear anaplasia which are easier to apply. In fact, most pathologists assign FNG based on nucleolar prominence at various magnifications of microscope which was the basis for ISUP nuclear grading. However, the ISUP nuclear grading does not apply to ChRCC.[5]

Few anecdotal studies have compared the FNG system and the grading system described by Paner *et al*.[12,14,19] The CTG respects the inherent nuclear abnormalities of ChRCC, as also the presence of areas of geographic crowding of nuclei. We conceptualize, based on our study, that the fluent application of CTG would require training on approximately 20–25 cases of ChRCC. Furthermore, the geographic innate crowding of nuclei adjacent to the tumor/renal capsule may lead to a false CTG-2 grading and should be kept in mind. The important feature not to be disregarded is that crowding has to be accompanied by nuclear (>3 times) and chromatin abnormalities. The majority of the cases in the present study were graded as CTG-1 (60%) with decreasing frequency to CTG-3 (15%). All sarcomatous cases were graded as CTG-3. These findings are similar to studies in the literature [Table 2].

In this study, the comparison between FNG and CTG yielded that these systems are comparable only at the ends of the grading spectrum, i.e., all FNG-1 and FNG-4 correspond to CTG-1 and CTG-3, respectively. However, ChRCC cases when graded by the CTG system were graded CTG-1 in almost 60% of cases. According to FNG, about 83.75% of cases were graded as FNG-2 and FNG-3. In contrast, with CTG all cases of FNG-2 were assigned CTG-1. The majority (55%) of the FNG-3 cases were downgraded to CTG-1 (54.54%) and CTG-2 (45.45%). Paner *et al*. compared FNG and CTG in their series and found that 93% of their cases were assigned FNG-2 or FNG-3, whereas by CTG 74% of cases were graded as CTG-1.[12] Finley *et al*. also demonstrate that majority of FNG-2 and FNG-3 cases downgrades to CTG-1 or CTG-2.[14] Thus, this study demonstrates that CTG provides an additional benefit in better stratification of FNG-2 and FNG-3 cases. This downgrade in CTG may translate into a modified clinical surveillance protocol as the stage-1 FNG-3 tumors might need a rigorous imaging follow-up schedule.[24] On ROC curve analysis, CTG demonstrated higher grading accuracy than FNG as AUC for CTG was more than that for FNG in the whole cohort as well as in nonsarcomatous cases. Finley *et al*. also reported similar findings with superior AUC for CTG in comparison to FNG.[14]

The value of CTG over FNG is clearly demonstrated when they are correlated with DFS. Although we found a significant correlation between FNG and DFS in ChRCC, this association was lost, when only the nonsarcomatous cases were included. Notably, the mean DFS of FNG-3 cases of ChRCC in our series was as high as 72.3 months. On the contrary, CTG-2 and CTG-3 had a DFS of 44.51 months and 14.64 months respectively, again reiterating the fact of a false overgrading of ChRCC by the FNG system. We also noted that there was no correlation between the FNG and disease-specific adverse events like metastasis or recurrence in nonsarcomatous cases. These findings are in concordance with a study by Delahunt *et al*.[11] Paner *et al*. also found that CTG had a superior prognostic value than FNG and aided in identifying cases with potentially greater risk for disease progression.[12] However, recently published studies validating CTG did not find a significant difference between the DFS of CTG-1 and CTG-2; on the contrary CTG-1 and CTG-2 when combined had a statistically significant different survival outcome as compared to CTG-3.[17,18] We were unable to validate this finding due to the lack of any disease-specific events in the CTG-1 subgroup. ChRCC has a better prognosis and is known to have a lower recurrence and metastasis rate; hence, only limited studies with longer follow-up have been able to adequately evaluate the CTG with other variables on a multiparametric analysis.[15] After excluding 12 sarcomatous cases, Paner *et al*. found that CTG was associated with the risk of adverse outcomes (P = 0.032), while FNG did not

show such association (P = 0.77). Further, Finley *et al.* reported that CTG was a significant predictor of outcome in univariate analysis (P = 0.025) when only nonsarcomatous cases were accounted for.[14] We demonstrate similar findings in nonsarcomatous cases in this series.

The retrospective nature of the current study induces the inherent biases associated with such studies. Forty-nine (62%) of our cases had been operated outside and hence, adequate clinical details were not available in many of these cases. This referral bias also contributes to the lack of optimal staging details. Due to these reasons, TNM staging could be done only in 38 cases (47.5%). The multivariate analysis could not be done due to the limited number of disease-specific events and follow-up in the rest of the cases. The way to circumvent this issue is either a meta-analysis of studies with adequate follow-up or to evaluate the outcome in this tumor with exceptionally larger sample size. However, a single institutional study with a large sample size and availability of follow-up information in a relatively good proportion of cases is the strength of this study. The shorter time-frame for the inclusion of cases and the histopathological review by an experienced genitourinary pathologist ensured an explicit cohort of ChRCC in this study.

CONCLUSIONS

Our study emphasizes the futility of applying FNG in ChRCC. CTG, on the other hand, is a feasible option and is a better predictor of DFS and disease-specific adverse events than FNG.

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Supplementary Table 1: Distribution of various histological parameters in the present study

Variables	Values
Age, Mean (range)	52.12 years (27-77 years)
Tumor size, Mean (range)	10.38 cm (3 cm-28 cm)
Sex, No. (%)	
Male	44 (55)
Female	36 (45)
pT Stages, No. (%)	
pT1a	6 (11.8)
pT1b	9 (17.6)
pT2a	2 (3.9)
pT2b	11 (21.6)
pT3a	18 (35.3)
pT3b	5 (9.8)
pT4	0
Nodal Stages, No. (%)	
N0/Nx	77 (96.2)
N1	3 (3.8)
Metastasis, No. (%)	
Mx	35 (43.8)
M0	40 (50)
M1	5 (6.3)
TNM Stages	
I	12 (31.6%)
II	09 (23.7%)
II	11 (28.9%)
IV	6 (15.8%)
Sarcomatous differentiation, No. (%)	
Absent	71 (88.8)
Present	9 (11.3)
Tumor Necrosis, No. (%)	
Absent	59 (73.8)
Present	21 (26.3)

Supplementary Table 2: Correlation of Fuhrman Nuclear Grade and Chromophobe Tumor Grade with Disease Free Survival

Grading System	Grades	Including sarcomatous cases							Non-Sarcomatous Cases						
		Correlation with DFS				ROC curve analysis for DFS			Correlation with DFS				ROC curve analysis for DFS		
		Cases	Events	Mean DFS	*P*	AUC (SE)	95% CI	*P*	Cases	Events	Mean DFS	*P*	AUC (SE)	95% CI	*P*
Fuhrman nuclear grade	Grade 1	1	0	NA	0.001	0.818 (0.067)	0.686-0.949	0.001	1	0	NA	0.272	0.724 (0.089)	0.550-0.889	0.063
	Grade 2	13	0	NA					13	0	NA				
	Grade 3	27	6	72.30					27	6	72.30				
	Grade 4	8	6	14.64					2	1	31.24				
Chromophobe tumor grade	Grade 1	29	0	NA	<0.001	0.919 (0.038)	0.884-0.994	<0.001	29	0	NA	<0.001	0.903 (0.046)	0.813-0.993	0.001
	Grade 2	12	6	44.51					12	6	44.51				
	Grade 3	8	6	14.64					2	1	31.24				

DFS: Disease-free survival, NA: Not Available