Indian Journal of Pathology and Oncology 2022;9(3):208–215

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Original Research Article

Nuclear morphometry is a superior prognostic predictor in comparison to histological grading in renal cell carcinoma: A retrospective clinico-pathological study

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ARTICLE INFO

Article history:
Received 02-05-2022
Accepted 17-05-2022
Available online 26-08-2022

Keywords:
Renal cell carcinoma
Nuclear morphometry
Fuhrman nuclear grade

ABSTRACT

Renal cell carcinoma (RCC) is a spectrum of clinico-pathologically distinct entities thereby making it difficult to accurately predict the clinical outcome. Subjectivity and lack of reproducibility in nuclear grade mandates use of more objective parameters like nuclear morphometry. Out of 219 cases of RCC, nuclear grading was done in 181 cases and digital morphometry was done in 100 cases. Nuclear grade and morphometric parameters were correlated statistically with the clinical outcome of the patients. Histological nuclear grade did not show statistically significant correlation with progression free survival (PFS). Higher values of morphometric parameters were significant predictors of PFS with a strong inverse correlation. Nuclear morphometry is a more reliable predictor of clinical outcome in patients of RCC when compared to histological grade and should be included in predictive model with other clinical and pathological parameters to accurately determine tumor behaviour.

1. Introduction

Renal Cell Carcinoma (RCC) represents about 2% to 3% of all visceral cancers and accounts for 85% of the renal cancers in adults.[1] RCC is a clinicopathologically heterogenous disease which had been previously classified differently by various systems until the most recent WHO 2016 classification.[2] Although our knowledge regarding the pathogenesis, morphology and molecular biology of RCC has significantly advanced, predicting the exact clinical outcome for individual cases is still challenging. The tumor stage and Fuhrman nuclear grade of the tumor have been considered as imperative factors determining the survival of these patients.[3–5] However, even after an accurate clinical staging, up to 30% of patients with RCC show variable disease progression after surgery. Moreover, clinico-pathlologically similar tumors with the same tumor stage may have altogether different tumor behaviour.[6] The Fuhrman nuclear grading on the other hand provides valuable information regarding the aggressiveness of the tumor but suffers from a major issue of subjectivity as well as difficulty in differentiating intermediate grades, resulting in the lack of uniformity in the nuclear grading system.[6,7] This warrants use of more objective methods for assessing distortion in nuclear shapes such as nuclear morphometry in predicting prognosis for RCC. The quantitative assessment of nuclear dimensions of the tumor cells is possible with the advent of computer imaging systems, which serves as a more reproducible method of predicting prognosis in renal cancer.[8–10] The purpose of the present study was to evaluate the role of nuclear morphometry in predicting disease free survival, and to correlate this variable with the

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https://doi.org/10.18231/j.ijpo.2022.051

clinicopathological prognostic factors in RCC.

2. Materials and Methods

The study included consecutive cases of resected renal tumors received in the Department of Pathology from January 2014 to May 2017 where patient's age >18 years. The clinical features and laboratory findings were recorded from the record maintained in hospital software system (e-hospital$^{@NIC}$) and patient's case files. Ethical clearance for the study was granted by institutional ethics committee. All the cases were reviewed for gross and microscopic features. Cases of clear cell and papillary RCCs were graded according to the Fuhrman grading system into four categories.[7] Grades were revised and a secondary nuclear area was designated as 'focal' if it was present in <25% area and given equal weightage if it was present in 25-50% tumor area. Staging of the tumor was done according to the AJCC TNM (8^{th} edition) staging system.[11] The follow-up data of the patients was recorded based on regular OPD visits by the patients as retrieved from the hospital records as well as the data procured through contact with the patient's family where necessary. Time of recurrence in the form of distant metastasis or local site recurrence and the time of death was noted where available.

Nuclear morphometry was assessed using a computer-assisted image-analyser system consisting of a microscope (Nikon Eclipse 80i) equipped with a high-resolution video camera (Nikon DXM1200F) and image analysis software (Image proplus, version 4.5). Representative area of the tumor showing the highest nuclear grade was marked on the slide taking care not to include areas of fixation or cautery artefacts, necrosis, haemorrhage and inflammation. For every case, 100 nuclei in the centre of the field in twenty high power fields were selected to exclude any selection bias. The images were captured with the video camera and the nuclear dimensions were evaluated using the sostware. Five morphometric descriptors were calculated for each case, i.e. the mean nuclear area (MNA), mean nuclear circumference (MNC), mean nuclear major diameter (MNMjD), mean nuclear minor diameter (MNMnD) and mean nuclear elongation factor (MNEF). Nuclear contours were outlined for each of the selected nuclei. Nuclear area was defined as the area enclosed inside the contour, the nuclear circumference was perimeter of the contour, and the major and minor diameters were the longest and shortest perpendicular diameters, respectively. Nuclear elongation factor was described as the ratio of major and minor diameter. A value of 1.0 indicated a perfect circular shape of the nucleus and any deviation from the circle would result in corresponding increase in value more than one. All statistical analyses were done using SPSS version 20.0 software. Correlation of qualitative factors with disease progression was done using chi-square test. Univariate analysis was done to analyse the prognostic significance of an individual factor. ROC curve analysis was used to evaluate the cut-off values and usefulness of morphological variables as a predictive marker of progression-free survival. Sensitivity, specificity and likelihood ratios were also calculated for each variable. All calculated P values were two-sided and P<0.05 was considered to indicate statistical significance.

3. Results

A total of 219 consecutive cases of resected adult renal tumors between January 2014 and May 2017 were studied. These included different subtypes of RCC including clear cell carcinoma (n=154), papillary (n=27), chromophobe (n=10), mucinous tubular and spindle cell (n=3) and collecting duct carcinoma (n=1). Benign tumors comprised of oncocytoma (n=8) and papillary adenoma (n=1). Other tumors included cases of angiomyolipoma (n=7), PNET (n=3), T-cell rich B-cell lymphoma (n=1), leiomyosarcoma (n=3) and adult Wilms (n=1). The age of patients ranged from 19 to 80 years with the median age of 53.4 years and a male to female ratio of 2.7:1. Majority of the patients (58.5%, n=128) presented with abdominal pain followed by hematuria (51.6%, n=113) and abdominal lump in (36.9%, n=81). The classical triad of all the three major symptoms was present in only 8.6% (n=19) of the patients. In the laboratory investigations, haemoglobin <10g/dl was present in 73.9% cases (n=162), serum creatinine >1.5mg/dl) was present in 28.3% cases (n=62) and deranged LFT including elevated values of serum total and direct bilirubin, transaminases or alkaline phosphatase was present in 10.5% cases (n=23). Grossly, the tumor size ranged from 1.5 to 22cm with the median size of 7cm. Most tumors were primarily located in the upper pole (n=103, 47%) followed by lower pole (n=71, 32.4%) and midpole (n=16, 7.3%). Focal necrosis involving <25% of the tumor area was seen in 36.5% cases (n=80) followed by moderate (25-50%) and extensive (>50%) necrosis seen in 18.7% (n=41) and 18.3% cases (n=40) respectively.

Fuhrman nuclear grading was done based on the conventional interpretation of nuclear parameters into four categories in 181 cases of clear cell and papillary RCCs. Thus, according to the original grades, there were 15 tumors (8.3%) with nuclear grade 1, 89 (49.2%) tumors of grade 2, 67 (37.0%) tumors of grade 3 and 10 cases (5.5%) with grade 4 nuclei including sarcomatoid differentiation. Each category was subdivided on the basis of proportion of other grades in the same tumor. According to the revised grades, there was no change in grade 1 tumors, however grade 2 tumors were reduced to 79 (43.6%), grade 3 tumors were increased to 74 (40.9%) and grade 4 tumors were increased to 13 (7.2%). Thus, nuclear grading was modified in 20 cases (Table 1). The AJCC staging was done in all cases of RCCs (n=194). Most of the tumors belonged to stage T1 (n=90, 46.4%) with size <7cm and confined to kidney while

19.6% tumors (n=38) were in stage T2 with size >7cm and confined to kidney. The second most common stage was found to be T3 (n=56, 28.9%) while only 10 cases were present in T4 stage. On grouping the TNM stages into four categories for prognostic derivations, most of the tumors constituted stage 1(n=87, 44.8%) followed by stage 3(n=58, 29.9%), stage2 (n=35, 18.0%) and stage 4 (n=14, 6.3%).

Follow-up data was available in 203 patients with a mean follow-up of 22.3 months (range 1 to 55 months). Of these, 33 patients were lost to follow-up and one was referred outside. A total of 19 patients died during the course of disease; two died in the immediate post-operative period while one died due to renal transplant-associated complications for the other kidney. Thus, follow up of >1year was available in 154 patients. Disease progression in the form of local site recurrence or distant metastasis occurred in 38 patients during a range of 11 to 20 months with a mean duration of 14.6 months and was confirmed either by imaging or re-excision surgeries. Recurrence in the form of distant metastasis occurred in lungs in 15 patients, skeletal in 5 patients, liver in 4 patients, retroperitoneal lymph nodes in 3 and bone marrow in one and brain in one patient. Local recurrence occurred in 3 patients of whom 2 presented with mass lesion in the residual kidney and one showed incisional site deposits. In the progressive group 10 patients had died, the mean duration of death from the time of surgery being 18.7 months (range 13 to 29 months) while in the non-progressive group, 6 patients had died (mean 24.6 months).

Morphometric analysis was performed in 100 cases of RCCs in which follow-up data of >1 year was available. The MNA, MNC, MNMjD and MNMnD showed significant correlation with histological type, tumour stage, nuclear grade, sarcomatoid differentiation and disease progression (Table 2). Higher values of these variables were significantly associated with presence of sarcomatoid histology, advanced tumour stage, higher nuclear grade and tumor recurrence. In contrast, MNEF showed no significant relation to any variable except sarcomatoid differentiation. Univariate analysis showed that higher values of MNA, MNC, MNMjD and MNMnD were significant predictors of progression-free survival with a strong correlation (higher value of r). Thus, higher the values of these predictors, lesser were the chances of disease-free survival. Higher nuclear grade and tumor stage were also significant predictor of progression though they showed lesser strength of correlation. Tumor morphotype did not show significant prediction of survival in this study (Table 3). The optimal cut-off for the sensitivity and specificity values and likelihood ratios for MNA, MNC, MNMjD and MNMnD, were 150 μm^2, 53 μm, 14 μm and 12 μm respectively. All of the variables were diagnostically useful with a likelihood ratios >1 (Table 4, Figure 1). On Kaplan Meier survival analysis, significant difference was present in the progression-free survival (PFS) in patients with morphometric values more than and less than the cut-off for each of nuclear variable (Figure 2). The mean PFS was not found to be significantly different in the different nuclear grades (p=0.3) especially between grade 2 and grade 3, though mean survival appeared to be significantly different between grade 1 and grade 4. However, the revised nuclear grades into different subcategories showed a significant difference in their PFS (Figure 3 , p=0.04). The stage of tumor showed significant correlation with PFS (p=0.02) however, the survival did not significantly differ in the different histological subtypes in the present study.

4. Discussion

The highest incidence of RCC is found between sixth and seventh decade as reported in the literature while the mean and the median age of incidence in the present study were 53.4years and 55.0 years respectively with a range of 19 to 80 years. In the present study, the incidence of RCC was found to be more in males with a male to female ratio of 2.7:1 which was similar to the gender ratio of 2-3:1 reported in literature.[12,13] The most common presenting symptom of patients in our study was that of abdominal pain while incidentally detected cases comprised of only 2.3% as compared to 66.7% asymptomatic patients reported by Nakatani et al. and 40% incidentally detected cases in a study by Sidharth et al.[14,15] The mean tumor size of 7 cm in the present study was close to 6cm and 5.3cm reported by Patard et al. and Violette et al. respectively.[5,16] Also, the most common location of the tumor was found to be upper pole in other studies similar to the present study.[15,16] In the histological subtype, clear cell RCC was the most frequently occurring tumor which was in concordance with the figures cited in the literature.[17,18] While microscopic tumor necrosis was identified in 73.3% of the cases in this study, it was observed in 30.5% and 40% of the tumors by sidharth et al and Stinga et al.[15,18] Though tumor necrosis has been shown to be an independent prognostic variable for RCCs, no such correlation was observed in our study.[19]

With respect to the Fuhrman nuclear grading of tumors, results in the current study were similar to other studies with most tumors displaying nuclear grade 2. After review of original grades, the revised grades showed an increase in grade 3 and grade 4 to 40.9% and 7.2% respectively while the proportion of grade 2 tumors were decreased (Table 1). This highlights the subjectivity of Fuhrman grading system and questions its accuracy I determining the tumor prognosis as also pointed out in few other studies.[6,7,20] Regarding the prognostic value of this parameter, Patard et al reported significant correlation of higher nuclear grade (3&4) with the survival in a multivariate analysis though grade 1 and 2 lacked independent prognostic significance.[5] Nakatani et al found a statistically significant1-year, 3-year and 5-year survival rates of 100%, 95% and 95% for grade

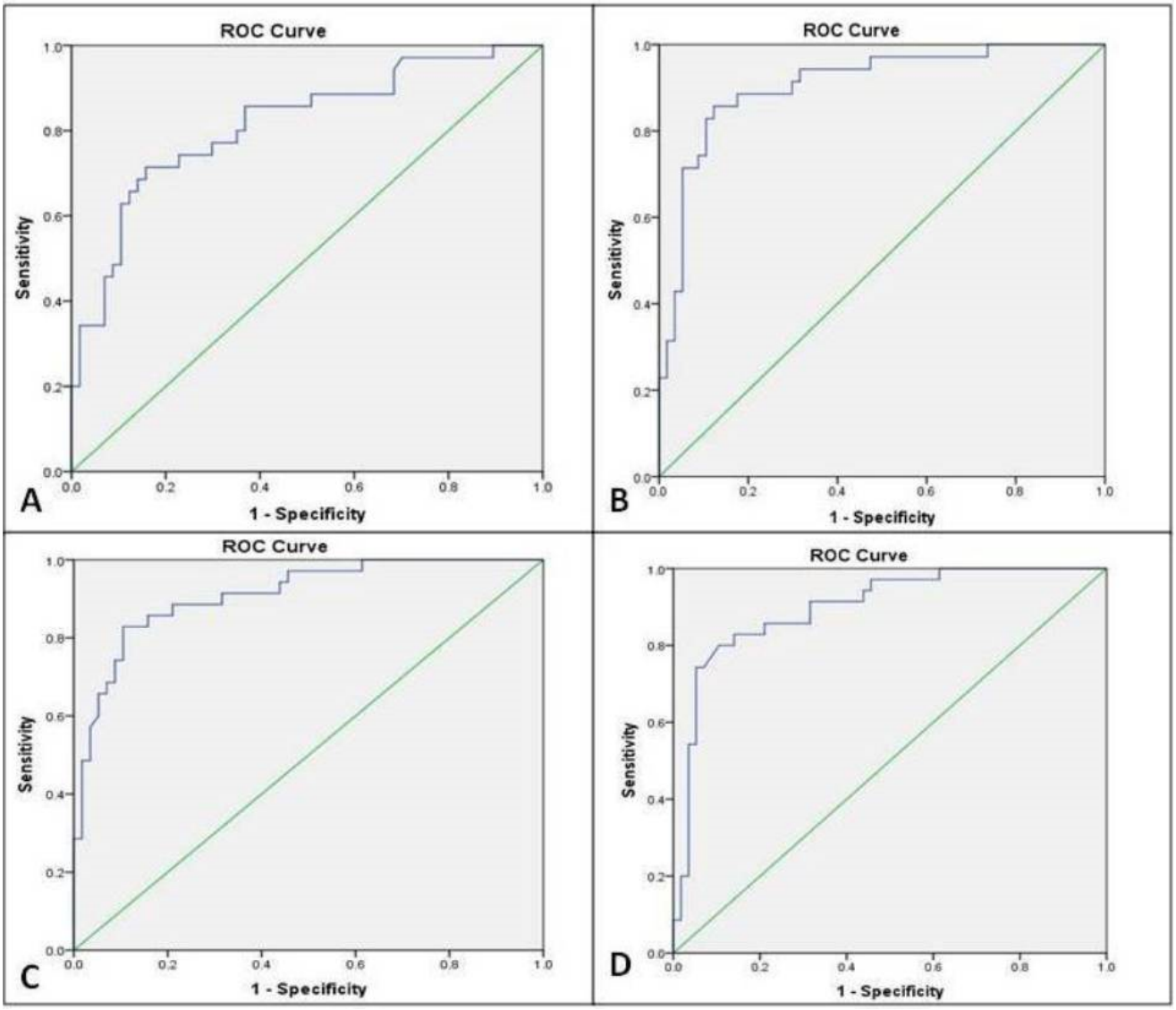

Fig. 1: ROC curves of morphometric variables as predictors of progression-free survival. **A:** Mean Nuclear Area (MNA), **B:** Mean Nuclear circumference (MNC), **C:** Mean Nuclear Major Diameter (MNMjD), **D:** Mean Nuclear Minor Diameter (MNMnD)

Table 1: Fuhrman nuclear grading of clear cell and papillary RCCs (n=181)

Fuhrman grade	Cases with original grade (%)	Subcategories	No. of cases	Cases with revised grade (%)
1	15 (8.3%)	1	15	15 (8.3%)
2	89 (49.2%)	2+focal 1	2	79 (43.6%)
		2+1	10	
		2	67	
		2+focal 3	5	
3	67 (37.0%)	3+focal 2	7	74 (40.9%)
		3+2	9	
		3	53	
		3+focal 4	2	
4	10 (5.5%)	3+4	2	13 (7.2%)
		4	9	

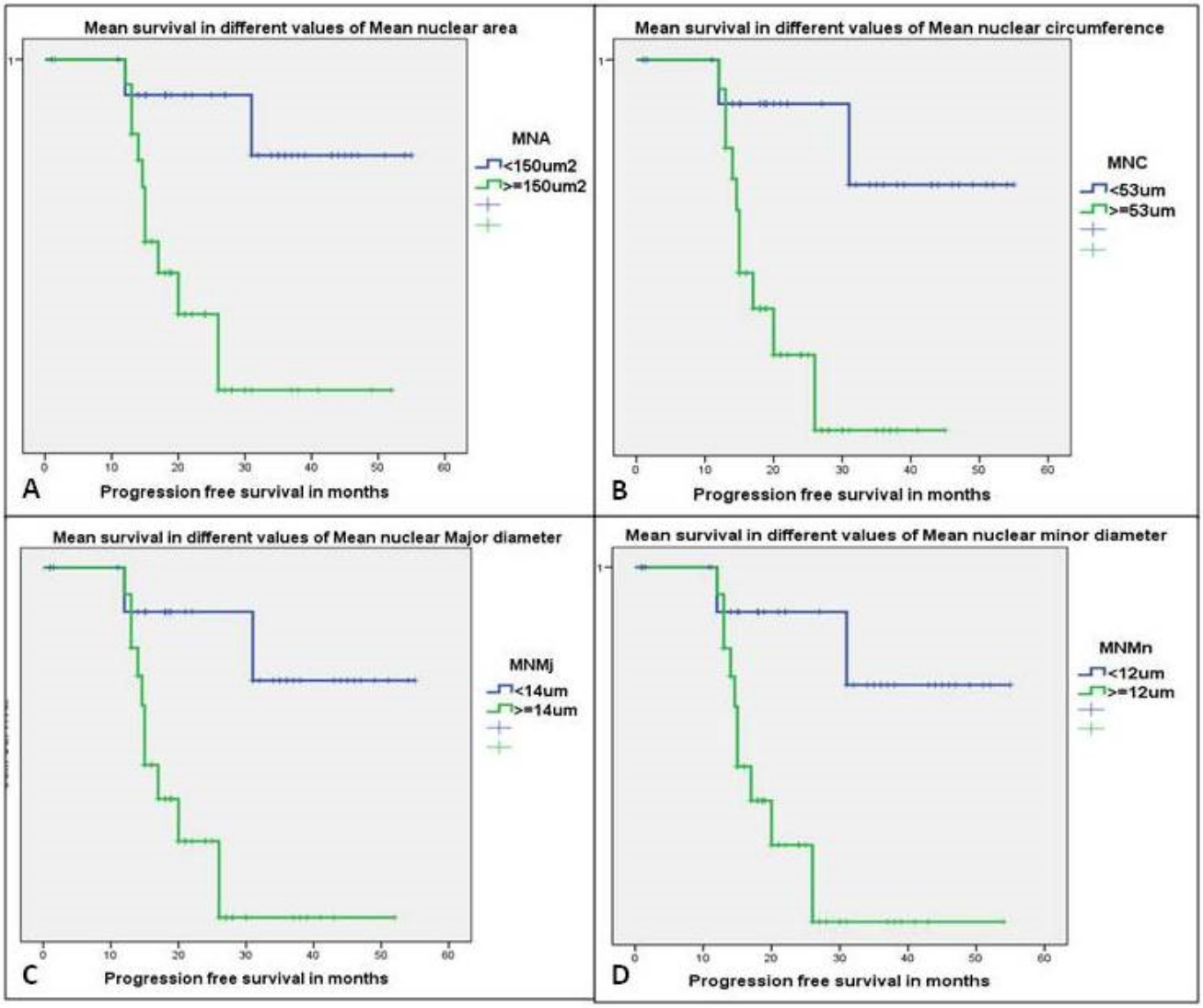

Fig. 2: Kaplan meier plots of the probability of progression-free survival (PFS) in patients with RCC. **A:** Mean PFS for tumors with MNA>= 150 μm^2 vs MNA<150 μm^2, **B:** Mean PFS for tumors with MNC>=53 μm vs MNC<53 μm, **C:** Mean PFS for tumors with MNMjD>= 14μm vs MNMjD< 14μm, **D:** Mean PFS for tumors with MNMnD>=12μm vs MNMnD<12μm

1 cases, 92.0%, 82.7% and 82.7% for grade 2 cases and 76.4%, 54.7% and 41.0% for grade 3 cases, respectively.[14] In the present study, Fuhrman grading did not show statistically significant difference in the PFS on Kaplan Meier survival analysis especially for the intermediate grades (Figure 3 a). On the other hand, the different categories of nuclear grade incorporating different nuclear features in the same tumor showed significant difference in the survival curves (Figure 3b). This shows that including more than one kind of nuclear area in the nuclear grade enhances its accuracy of prediction though this may not be feasible if more than two cytologically different areas are present in the tumor which is not so uncommon for RCC.

Tumor staging of RCC has been established as the most consistent and powerful predictor of prognosis.[4,21,22] In the current study, most of the tumors (46.4%) presented in T1 followed by T3 similar to the observations of Patard et al and Violette et al.[5,16] Also, the TNM stage showed statistically significant prediction of survival on univariate analysis in concordance with the findings of Patard et al[5] (Table 3).

Quantitative assessment of nuclear morphometry with computer imaging systems were done in various studies and correlated with the already established prognostic factors of renal cell carcinomas.[8–10,23] According to Gutierrez et al, MNA, MNMjD and MNMnD and MNC moderately correlated with pathologic stages and highly correlated with Fuhrman nuclear grade. However, correlation between

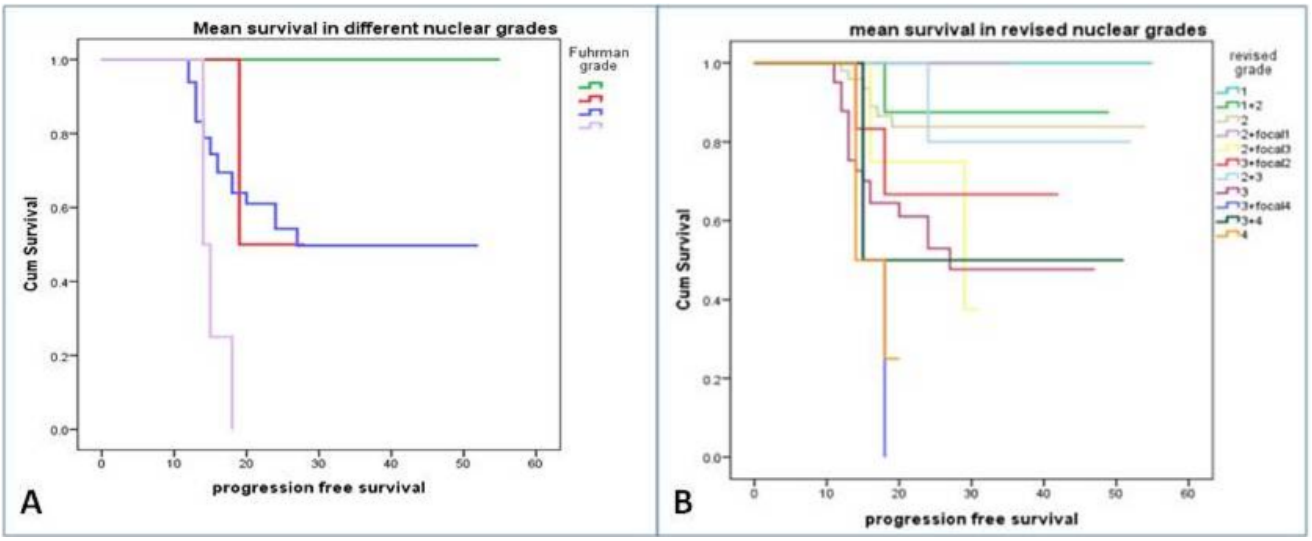

Fig. 3: Kaplan Meier plots of the probability of progression-free survival in different nuclear grades. **A:** Original nuclear grades, **B:** Revised nuclear grades

Table 2: Correlation of morphometric data with histopathological findings and disease status

Variable	Mean (SD)	Total n=92(%)	MNA (μm^2)	MNC (μm)	MNMjD (μm)	MNMnD (μm)	MNEF x10 (%)
Gender	M	74 (80.4)	174.9 (47.6)	59.3 (13.2)	15.2 (2.6)	12.4 (2.0)	12.4 (0.7)
	F	18 (19.6)	148.5 (30.1)	51.9 (10.0)	13.6 (2.0)	11.1 (1.9)	12.3 (0.8)
Histological Subtype	Clear cell	81 (88)	165.6 (39.7)	58.0 (12.9)	14.7 (2.4)	12.9 (2.0)	12.3 (0.7)
	Papillary I	1 (1.0)	180.8	53.0	16.0	12.4	13.1
	Papillary II	7 (7.6)	219.4 (84.8)	59.9 (15.3)	17.0 (3.9)	13.4 (2.7)	12.9 (0.6)
	Chromophobe	3 (3.4)	159.3 (45.8)	50.9 (9.9)	14.4 (2.0)	11.7 (1.3)	12.7 (0.3)
Fuhrman grade	1	10 (10.9)	132.2 (17.1)	48.9 (9.3)	12.0 (2.1)	9.9 (1.8)	12.2 (0.7)
	2	41 (44.6)	145.9 (23.0)	51.9 (6.2)	13.6 (1.4)	11.3 (1.5)	12.3 (0.7)
	3	32 (34.8)	199.6 (44.5)	66.5 (13.5)	16.7 (2.0)	13.5 (1.2)	12.4 (0.8)
	4	6 (6.5)	240.9 (37.7)	71.0 (16.4)	18.9 (2.3)	15.3 (1.8)	12.4 (0.5)
Stage	1	51 (5.5)	157.5 (34.5)	55.5 (9.8)	14.3 (2.1)	11.5 (1.8)	12.3 (0.7)
	2	18 (19.6)	162.8 (38.5)	56.3 (13.4)	14.5 (2.3)	11.8 (1.7)	13.1 (0.7)
	3	19 (20.7)	185.8 (57.4)	64.2 (16.2)	15.8 (2.9)	12.9 (2.1)	12.2 (0.6)
	4	4 (4.3)	235.5 (58.6)	68.4 (18.7)	18.6 (3.4)	15.4 (2.3)	12.2 (0.8)
Sarcomatoid diff	Present	2 (2.2)	245.8 (45.4)	94.5 (12.4)	19.4 (2.6)	16.8 (2.0)	12.3 (0.7)
	Absent	90 (97.8)	168.8 (43.2)	57.5 (10.2)	14.8 (2.5)	12.1 (1.9)	11.6 (0.7)
Disease Progression	Present	35 (38.0)	207.8 (46.4)	66.8 (14.2)	17.1 (2.1)	13.8 (1.6)	12.5 (0.7)
	Absent	57 (62.0)	146.6 (25.2)	52.4 (8.4)	13.5 (1.6)	11.1 (1.6)	12.3 (0.7)

Table 3: Univariate analysis of morphometric variables and clinicopathological prognostic factors as predictors of progression

Variable	p-value (disease-free survival)	r –value (strength of correlation)
MNA	<0.001	-0.48
MNC	<0.001	-0.36
MNMjD	<0.001	-0.48
MNMnD	<0.001	-0.52
MNEF	0.4	0.07
Nuclear Grade (revised)	0.02	-0.26
Stage	0.04	-0.09
Histological subtype	0.2	-0.09

Table 4: ROC analysis of morphometric variables as predictors of progression-free survival

Nuclear variable	Cut-off value (μm)	Sensitivity (%)	Specificity (%)	Likelihood ratio	P-value
MNA	150	94.3	66.7	2.83	<0.001
MNC	53	85.7	63.2	2.32	<0.001
MNMjD	14	91.4	66.7	2.74	<0.001
MNMnD	12	91.4	66.7	2.74	<0.001

MNEF and Fuhrman nuclear grade, pathologic stage, and tumor size were not statistically significant.[23] In a study by Nativ et al, MNEF and MNA were the best predictors of disease free survival as compared to other variables such as age, gender, tumor size and histological subtype. The 5- and 10-year survival rates were higher for patients with MNA <32μ^2compared with those with MNA >32μ^2(89% and 62% versus 50% and 40%, respectively).[8] In the present study, the higher values of the different morphometric variables were significantly related to sarcomatoid differentiation, advanced tumour stage, higher nuclear grade and tumor recurrence. MNEF showed no significant relation to any variable except sarcomatoid histology similar to the studies done by Ozer et al and Monge et al.[10,24] Thus nuclear ellipticity did not play a significant role in deciding the aggressiveness of renal cell carcinoma. Also, higher values of MNA, MNC, MNMjD and MNMnD were significant predictors of PFS with a strong inverse correlation (Table 3). On Kaplan Meier survival analysis, there was significant difference in the survival of patients with morphometric values greater than cut-off value as compared to those with values lesser than the threshold (Figure 2). These findings were similar to those of Nativ et al who concluded that nuclear morphometry was prognostically superior to conventional nuclear grading in patients with localised RCC.[8]

5. Conclusion

RCC includes a myriad of entities such that it is clinically very important to accurately identify the high risk patients. Although a host of studies are available in the literature describing and identifying various prognostic factors, none of them provide a precise and uniform information regarding the individual tumor behaviour in the long run. The prognostic significance of nuclear grade in distinguishing the risk groups for recurrence is limited by its subjectivity and irreproducibility, particularly in the intermediate grades, and further affected by the presence of different intratumoral cytological areas in RCCs. Thus, use of the objective and quantitative morphometric approaches is the need of the hour and needs to be promoted in routine practices. The significant association of the higher morphometric values of the tumor nuclei with the various clinicopathological features as well as the PFS demonstrated in this study is not surprising since these nuclear variables have been traditionally considered as the key feature of anaplasia. Though the findings of this study only provide preliminary findings, further prospective studies with long follow-up data are mandatory to consolidate these results and justify the incorporation of nuclear morhometry along with stage and grade in the prognostic model of RCC.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Agrawal S, Jain N. Nuclear morphometry is a superior prognostic predictor in comparison to histological grading in renal cell carcinoma: A retrospective clinico-pathological study. *Indian J Pathol Oncol* 2022;9(3):208-215.