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Renal Tumours in Adults with Correlation between Fuhrman Grading and Proliferative Marker

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ABSTRACT

Background: Definite data regarding the incidence and distribution of renal tumours in eastern India is not known. For better management, as it is essential to identify patients with poor prognosis, prognostic factors like stage, nuclear grade and their relationship to molecular markers are also unclear in this region. The purpose of our study was to assess the spectrum of adult renal tumours with respect to age and sex and to correlate Fuhrman nuclear grading with Ki-67 labeling index in a tertiary care hospital in eastern India.

Methods: All adult patients with kidney tumour referred to our hospital who were preoperatively diagnosed and undergone surgical resection were included. Distribution of histological subtypes of kidney tumours according to age and sex were done by Hematoxylin and Eosin stain. Fuhrman grading, performed by ocular morphometry and derivation of Ki-67 labeling index (LI), were done in malignant cases only. Correlation of Fuhrman grading and KI-67 LI were done individually.

Results: Among total 36 cases, 3 were benign and 33 were malignant. Among the malignant cases: Fifteen, twelve, four and two cases were of Fuhrman grade I, II, III, IV with mean Ki67 labeling index of 6.5, 18.2,44 and 76 respectively. Statistical correlation between mean Ki-67 LI and Fuhrman grading revealed significant correlation between Grade I and II, II and III and combined Grade I,II and III,IV tumours.

Conclusion: Malignant Kidney tumours, especially, grade I RCC were commonest tumour. Fuhrman grading correlated well with Ki-67 labeling index. A 2-tier system for grading is proposed for better correlation with proliferation.

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Introduction

The majority of renal neoplasms are epithelial in origin and malignant in nature. Based on the historical concept of their derivation from adrenal rests in kidney they were called hypernephroma. Renal Cell Carcinoma (RCC) is a highly unpredictable neoplasm with a tendency to recur, metastasize or cause death many years after initial treatment. Although surgery is the only proven therapy, with expansion of the treatment horizon, it is imperative that the patients with high risk of tumour progression should be identified (1). Malignant tumours of the kidney (renal pelvis and parenchyma) represent

2-3% of all cancers, with the highest incidence occurring in Western countries. Eight percent of them involve the parenchyma and 85% of them are renal cell carcinoma (1). Several prognostic factors for RCC have been validated by a number of independent studies. Age of the patient is an independent prognostic factor (25-27). Several studies have shown a trend of increasing tumour incidence with age. However, the morphology and clinical behaviour of tumour with respect to age of the patient, as questioned by many, is still equivocal (26, 28).

Other important prognostic factors are tumor stage, histologic grade, microscopic variant, lymphocytic infiltration, and DNA ploidy (2). Among the well-established prognostic factors, tumor stage is the most important. There were various staging systems of RCC, but TNM system proposed by UICC and AJCC, are commonly used. The 5-year survival rate following nephrectomy is 60-80% in stage I, 40-70% in stage II, 10-40% in stage III, and 5% or less in stage IV (3). Prognostic factors like microscopic tumour necrosis and nucleolar prominence are receiving renewed attention in view of few large studies (38). Nuclear grade of the RCC as determined in microscopic sections is not only an important predictor of survival; it strongly correlates with surgical staging and also maintains statistical validity independent from it. Various grading systems were proposed, however, Fuhrman's Nuclear Grading system (4) is now widely accepted method of histologic grading because various studies show that this system correlates well with survival prediction (4–8).

On the other hand, as with many cancers, prognostic evaluation have undergone a paradigm shift the recent years and emphasis is now given to relatively subtle histologic features, e.g. angiogenesis and molecular markers. The rate of cell-proliferation is thought to have a major influence on malignant tumor behavior and it has been shown in different tumors that proliferative activity correlates with metastatic potential, tumor recurrence and in some cases overall prognosis(9). Ki-67 is a nuclear protein that is encoded by the MKI67 gene. Ki-67 is an excellent marker to determine the growth fraction of a given cell population (10–16).

Definite data regarding the incidence of renal tumours is not available in India and there is no kidney tumour registry. Subsequently, any data regarding the histological characteristics, distribution of cases according to age and correlation between stage, nuclear grade and proliferative markers are also deficient.

Here, in this prospective observational study, we attempted to study the spectrum of adult renal tumours in this institution with respect to age and sex. The roles of proliferative marker (Ki67) in patients of RCC and their relationship, if any, with the nuclear grades of these tumours were also assessed.

Materials and Methods

The prospective and observational study was done in Pathology Department of I.P.G.M.E. &R. and SSKM hospital, Kolkata, India (A tertiary care super speciality hospital) for the period of 2 years (June 2010 to June 2012). The study population was all adult patients with kidney tumour referred to SSKM Hospital. Total number of cases received was 36. Adult patients of preoperatively diagnosed cases who have undergone surgical resection of tumour were included in the study. The methods used in our study were to find the distribution of different histological subtypes of adult kidney tumours in population with respect to age and sex by doing Haematoxylin & Eosin stain. After that, nuclear grading (4) was done according to the Fuhrman grading system wherever applicable. Immunohistochemical staining and Ki-67 labelling by MIB-1 antibody was done in malignant kidney tumours and the relationship between Ki-67 labelling and nuclear grading with histological grade and subtype of

Renal Cell Carcinomas were evaluated.

After taking a valid consent from the patients a detailed history was taken from each of the patients. Their age and sex were recorded. Symptoms (like hematuria, lump in abdomen, and pain in the back) and signs (like ballotment) were elicited. All the cases were radiologically diagnosed before surgery. After operation Radical Nephrectomy, specimens were weighed, measured and dissected in standard method. The slides were stained by hematoxylin and eosin (H&E) stain by standard protocol.

Fuhrman Nuclear Grading (4) was done on histological smears of the epithelial cells with the aid of an ocular morphometer (ERBA, Japan) attached to the eyepiece (10X) of a microscope (Olympus MLX-B) using a 40X objective (total magnification 400X).In average 500 random nuclei were assessed for each case. The nuclei were graded according to original description of Fuhrman et al. (4) which is as follows:

Grade 1: Round uniform nuclei approximately 10 μm in diameter with very small or absent nucleoli.

Grade 2: Slightly irregular nuclear contours and diameters of approximately 15 μm with nucleoli visible at ×400.

Grade 3: Moderately to severely irregular nuclear contours and diameters of approximately 20 μm, with large nucleoli visible at ×100.

Grade 4: Nuclei similar to grade 3 but also multilobular, multiple, or bizarre nuclei and heavy clumps of chromatin.

Immunohistochemical staining for Ki67 was done by Polymer chain 2 step indirect technique using monoclonal antibodies to Ki-67. Formalin-fixed paraffin-embedded sections (4 μm) in poly-l-lysine coated slides were used for standard streptavidin-biotin-peroxidase-diaminobenzidine immunohistochemical technique. Negative controls were performed by omitting the primary antibody. A Labeling Index (LI) for Ki-67 was derived by dividing the number of positively stained cell nuclei by the total number of nuclei counted in areas of maximal proliferation (17).

Data was tabulated, analyzed and a grand chart was prepared. Statistical tests of significance were done by unpaired student '*t*' test and *P* value<0.005 was considered significant.

Result

Total numbers of cases were 36. Thirty-three of them were malignant and 3 benign. Among the benign cases, 2 cases were of classical variety of angiomyolipoma. Both the cases were discovered incidentally during ultrasonography of whole abdomen for non-urological reason. Both the patients were male aged 58 and 80 years. We have received a single case of adult variant of congenital mesoblastic nephroma (aCMN) in a female-aged 32 years. Among the malignant cases 30 were of clear cell carcinomas of kidney of various grades (Fig. 1 and 2). 2 were papillary renal cell carcinomas and a single case of sarcomatoid renal cell carcinoma.

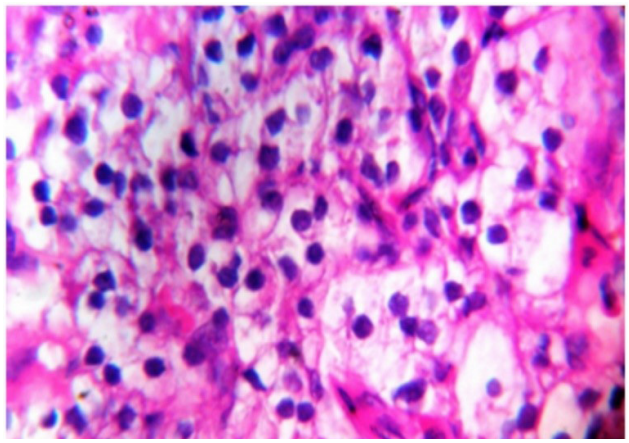

Fig. 1
Clear cell renal cell carcinoma. Fuhrman grade I. (H&E, 1000X)

Most of the cases were found in the 51 to 60 years age group whereas most case of clear cell carcinomas was concentrated in age group 41 to 50 years. Two cases of papillary carcinomas were found in a 37-year-old male and a 57-year-old female. Two cases of angiomyolipoma were

discovered incidentally in a 58 years and 80 years old male, whereas an adult variant of mesoblastic nephroma was discovered in a 32-year-old female. A single case of Sarcomatoid carcinoma of kidney was found in a 57-year-old male. Among the 36 patients 13(44%) were female and 23(56%) were male (M: F=1.7:1).

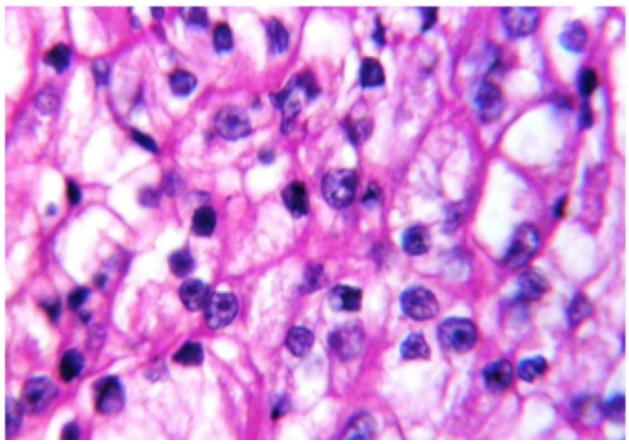

Fig. 1
Clear cell renal cell carcinoma. Fuhrman grade III. (H&E, 1000X)

Table 1 represents distribution of cases according to Fuhrman grading. Most of the cases (15/33) were in grade I; followed by 12 cases in grade II and 4 and 2 cases in grade III and IV respectively.

Table 2
Distribution of renal cell carcinoma cases according to Fuhrman Grading (n=33)

Fuhrman grade	Number of cases
I	15
II	12
III	4
IV	2

Mean Ki67 labeling index of malignant cases according to Fuhrman grading system is represented in Table 2. In case of clear cell carcinoma kidney Mean labeling index for Grade I, II, III and IV were found to be 6.5, 18.2, 44 and 73 respectively. Figure 3 and 4 demonstrates KI 67 LI of Fuhrman grade I and III tumours, respectively. Two cases of papillary carcinoma

Table 2
Distribution of renal cell carcinoma cases according to Fuhrman Grading (n=33)

KI 67 Labeling index	Fuhrman Grade I	Fuhrman Grade II	Fuhrman Grade III	Fuhrman Grade IV
cRCC	6.5	18.2	44	70
PapRCC	-	20.5	-	-
Sarcoma-toidRCC	-	-	-	76

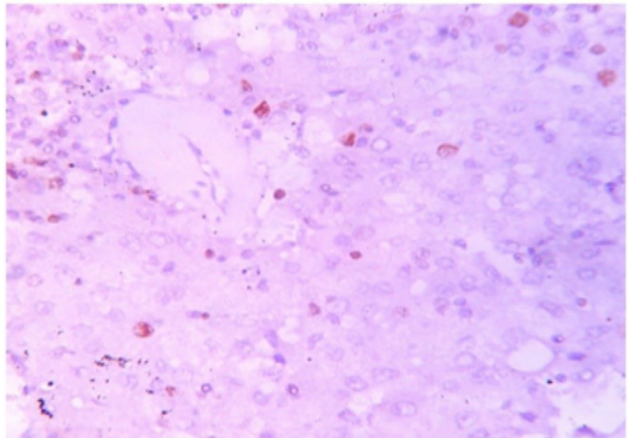

Fig. 3
KI 67 Labelling Index of grade I clear cell renal cell carcinoma

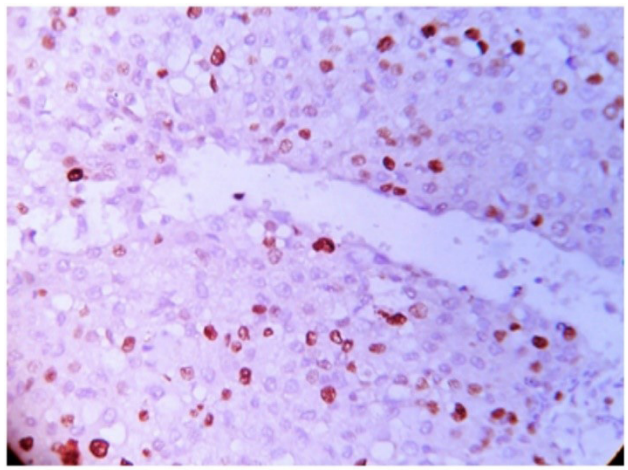

Fig. 4
KI 67 Labelling Index of grade III clear cell renal cell carcinoma

kidney were found to be of Fuhrman grade II with mean Ki67 labeling index of 20.5%. The

Table 3
Correlation between Fuhrman grading and Ki labeling index (unpaired t-test) (*P* value<0.005) (n=33)

Correlation between Fuhrman grading and Ki Labeling index	*P* value	Remarks
I and II	0.0000001566	Significant
II and III	0.0003647	Significant
III and IV	0.045	Not significant
I and II with III and IV	0.00000000128	Significant

single case of sarcomatoid carcinoma of kidney had a Fuhrman grade of IV with Ki67 labeling index of 76%.

There was significant correlation of mean Ki67 LI between grade I and II & II and III. A very significant correlation was found when combined results of grade I & II (together taken as low-grade tumours) with III & IV (together taken as high grade tumours) were compared. However, correlation between grade III and IV renal cell carcinomas with their mean Ki67 labeling index was not found to be significant (Table 3).

Discussion

Just two and a half decades ago, adult renal cell neoplasms, i.e., those arising from the renal tubular epithelium, were subdivided into two major subtypes: "clear cell carcinoma" and "granular cell carcinoma." Subsequent detailed morphologic and/or cytogenetic studies have resulted in the recognition of several distinctive subtypes of adult renal epithelial neoplasms. Cancer of the kidney is the 12th most common cancer in men and 17th in women. According to SEER database 2006, of the 28,560 persons with adenocarcinoma of kidney, 26,490(92%) were renal cell carcinomas (M: F=1.7:1) of various histological types (18). In our study, 36 patients were included of who 33 had malignant disease.

Angiomyolipoma (AML) is the most common benign mesenchymal neoplasm in kidney (19). They account for approximately 1% of all surgically removed renal tumors. AMLs are now included under the umbrella term "neoplasms of the perivascular epithelioid cells," (PEComas) (20).Classic AML may occur either sporadically or in association with tuberous sclerosis complex (TSC).Approximately 4.5% of AMLs may not show identifiable macroscopic fat and are indistinguishable from RCC on imaging studies alone (21). In our study, both cases were of classic triphasic type. (M: F=1:1). Mixed epithelial and stromal tumors (MEST)/ Mesoblastic nephroma(MN) are rare complex renal neoplasms composed of a mixture of cystic and solid components. It is the most frequent benign renal tumor in the childhood (22). Up to 2009 total 78 cases were reported by various authors (22). MN is poorly characterized in adults. In a study by Montironi and colleagues, the mean age of the patients with MEST was reported to be 46 years, with the female to male ratio of 6 to 1 (23). The most important aspect is the occasional malignant transformation to sarcoma or carcinoma. In our study, a single case was found incidentally in a female patient.

Renal cell carcinoma (RCC) is a very heterogeneous disease with widely varying prognosis. Prognostic factors in RCC include anatomical (TNM classification, tumor size), histological (Fuhrman grade, histologic subtype), clinical (symptoms and performance status), and molecular features. Not all these features are accurate when used alone. Therefore, an increasing number of prognostic models or nomograms that include several combined prognostic features have been designed in order to improve predictive accuracy.

In southern Asia, in preliminary study in Pakistani population, 94% of all renal neoplasms

were malignant and among the malignant ones 87.2% were renal cell carcinomas (24). In our study, representing a population from eastern India, we have found that 91.6% cases of renal neoplasms are malignant. Of them, 90.9% cases are clear cell (Fig. 1 and 2), 6.0% cases are papillary and 3.0% are sarcomatoid RCC.

Age at diagnosis is an independent prognostic factor for renal cell carcinoma. In numerous studies it was published that incidence, clinical presentation and pathological prognostic factors affecting disease outcome of RCC is different in young adults (<40 years) and the older population (25-27). According to the authors of SEER survival monograph the greatest incidence of renal tumour in adults occurred in the 60-69 age group (18). When comparing younger to older patients, there was a lower male-to-female ratio lower stage and fewer clear-cell carcinomas but more papillary carcinomas respectively (26, 27). Young patients (<40 years) were also reported to have lower 5-year-progression-free survival (26). Prognostic factors for renal cell carcinomas were not different between two age groups (<40 vs >40 years) and across sex (28). In our study 5(13.8%) of the 36 patient were under 40. Their male to female ratio was 1:5. Incidence of clear cell carcinoma was 80% in <40 years age group which is less compared to the >40 years group (88.8%).

Grading for renal tumours by nuclear morphometry alone was 1st proposed by Skinner and associates in 1971(29). Furhman et al. simplified it providing a good working classification of nuclear grading (based on nuclear size, irregularity of the nuclear membrane, and nucleolar prominence) for RCC, which correlated well with prognosis and survival (4). In 2005, A nationwide series from Iceland reported that nuclear grading is important and strongest prognostic factor in RCC (30). As demonstrated in another large series of RCC patients, Fuhrman grading has prognostic utility for clear cell RCC; for papillary RCC, grading should be based upon nucleolar size and that Fuhrman grading is inappropriate for chromophobe RCC (31). The presence of tumour necrosis represents an independent predictor with respect to metastasis-free and overall survival in patients with clear cell and papillary RCC (40). Delahunt et al. pledges the importance of microscopic tumour necrosis as an additional prognostic factor when combined with nucleolar prominence (38). The most relevant drawback of the Fuhrman nuclear grading system is subjectivity and lack of efficacy in establishing prognostic groups (32). Optimum interobserver agreement was reached by collapsing the 4 tired system of classification into a 3 tired and then a 2 tired one while preserving the independent prognostic value of nuclear grade (6). In our study a very significant correlation with Ki 67 LI was found when combined results of grade I & II (together taken as low grade tumours) with III & IV (together taken as high grade tumours) were compared. (Table 2 and 3)

Cellular proliferation index is a predictive variable for biologic aggression of renal cell malignancy and therefore prognosis. Ki-67 is a nuclear protein that is encoded by the MKI67 gene. Ki-67 is an excellent marker to determine the growth fraction of a given cell population. The fraction of Ki-67-positive tumor cells (the Ki-67 labeling index) (Fig. 2) is often correlated with the clinical course of a variety of cancer including RCC (33). When the patients were sub grouped according to Ki-67 indices, they had significantly worse prognosis even in the same nuclear grade (10). After analyzing 741 kidney tumour specimens for Ki-67 expression, a group of researchers found high level of correlation among tumour cell Ki-67 expression and coagulative tumor necrosis with prognosis (11). Several recent studies suggest that Ki-67 expression could serve as an independent predictor of DFS in localized cRCC on multivariate analysis and that it may represent the true "molecular grade" of cRCC (34). But, Gelb AB and associates in their study, found nuclear grade and tumor size

were to be independent predictors of survival but not MIB1 LI (35). Bui et al. in their study on 244 patients treated with nephrectomy for clear cell RCC reported high Ki67 staining was highly significant for stratifying patient groups defined by T stage and Fuhrman grade (14). Similarly, nuclear stainings of Ki67, p21, and survivin were significantly associated with disease-specific survival and increased predictive ability in a multivariate model including T-stage and Fuhrman grade (36).

Sakai et al. in analysis of 12 markers found that, Ki-67, expression was significantly associated with several conventional prognostic factors including nuclear grade (37). In China, p53 and Ki67 double-positive expression could be used as independent predictor of disease-specific prognosis of RCC, which might provide the basis of individualized adjuvant treatment for each patient (39). So far, 5 validated diagnostic markers are able to differentiate between ccRCC and pRCC and Ki 67 is one of them. Few independent prognostic markers have been identified for pRCC in single studies, compared to numerous biomarkers identified for the more common cRCC (15). We have also found significant correlation between Fuhrman grade and Ki67 LI in cRCC cases (Table 2). No correlation was possible in case of Papillary and sarcomatoid RCC due to small sample size.

Conclusion

Malignant kidney tumours are common in 41 to 60 years age group in our institution and most of them are grade I clear cell renal cell carcinomas. Fuhrman's nuclear grading correlates well with Ki67 LI in clear cell renal cell carcinomas. Reduction of Fuhrman grading in two tier system (high grade/low grade) appears to provide more significant correlation with Ki67 LI. This study was done on small number of cases. A larger prospective study, with wider spectrum of markers would be more useful to determine the prognostic value of proliferative markers with respect to Fuhrman Grading.

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Abbreviations:

RCC- Renal cell carcinoma
cRCC- Clear cell renal cell carcinoma
papRCC- Papillary renal cell carcinoma
sarcRCC- Sarcomatoid renal cell carcinoma
AML- Angiomyolipoma
aCMN- Congenital Mesoblastic Nephroma(adult variant)
Ki 67 LI- Ki 67 Labeling index
UICC- Union for International Cancer Control
AJCC- American Joint Committee on Cancer

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