A study on the histomorphological correlation of renal tumors using Fuhrman grading and TNM Staging

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Abstract

Renal cell carcinomas are aggressive tumors which are stratified based on Fuhrman grading and TNM staging for prognosis. The total number of cases of renal cell carcinomas used for this study was 40. Clinicomorphological variables were correlated. Clear cell carcinoma accounted for maximum number of lesions. The clinical manifestations included hypertension, flank pain; flank mass but all features were noted only 10 cases. All the cases showed a male preponderance and common age group was 4th to 6th decade. Furhman Grade and TNM stage can be used as single independent prognostic factors. Clear cell and papillary renal cell carcinomas were low grade tumors with PT1-3 and Furhman grade I or II. Sarcomatoid and undifferentiated carcinomas were high grade tumors with PT4 and furhman grade IV. There was no positive correlation between necrosis of the tumor and Furhman grade, most patients had Furhman grade I or II. There was no correlation between histologic subtype and necrosis. Size alone is not an independent predictive prognostic factor. Microvessel involvement and peripelviceal sinus involvement was seen in sarcomatoid variant. None of the cases in this study showed adrenal involvement.

Keywords: Reanl cell carcinoma, Furhman Grade, TNM stage, Immunohistochemistry

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Introduction

Renal cell carcinomas are highly aggressive tumours with a wide variety of clinical manifestations, histomorphological features and varied prognosis depending on the grade and stage. Renal cell carcinomas are now considered to be a multifactorial and heterogenous group of disease with multiple gene mutations, deletions and translocations involved.

Many staging systems have been introduced such as TNM staging,(1) Fuhrman Grading,(2) AJCC staging,(3) ISUP grading,(4) as there is no single independent comprehensive staging system for prognostic identification.

The histologic subtypes of RCCs, according to the 2004 World Health Organization (WHO) classification, include clear cell, papillary, chromophobe, collecting duct and unclassified.(5) The mean age at presentation is often between 40-60 yrs, with males being more commonly affected than females. Often show evidence of minimal residual disease after one year.

However, few prognostic factors including tumor-node-metastasis (TNM) stage, Fuhrman's grade and tumor size are undisputed prognostic factors for RCC.(6)

The TNM classification system stratifies patients according to anatomic factors such as size, local extent of the primary tumor, involvement of locoregional lymph nodes, multifocality, bilaterality and the presence of distant metastases.(7,8)

The Fuhrman grading system is based on assessment of the uniformity of nuclear size, nuclear shape and nucleolar prominence.(2) The Fuhrman grading system has been found to correlate to metastasis with grade 1 tumours having a statistically significant lower metastases rate compared to those with grade 2 to 4.(2) A three tired system has been shown to be an independent predictor of survival.(9,10)

Renal cell carcinomas morphological features will be correlated with Fuhrman grading and TNM staging.

Materials and Method

The current study carried out department of pathology, Narayana Medical College & Hospital, Nellore, AP. The exclusion criteria was to exclude Wilm's tumour, Renal cell adenoma and metastatic tumours to the kidney.

All renal cell carcinomas were taken for this study. Formalin fixed gross pathological specimens of 40 renal cell carcinomas were studied. The method of fixation is as for routine histopathologic specimen and no special fixative was used.

4 microns sections were taken from these paraffin embedded tissue blocks. Histological sections stained with Haematoxylin & Eosin were used.

Gross photographs were taken. Histologic subtype categorised and Furhman grading was done. TNM staging was done for cases with available status. Pathologic staging for metastasis for most of them was not possible.

Table 1: Fuhrman Grading[2]

Grade	Nuclear size	Nuclear shape	Chromatin	nucleoli
1	<10microns	round	Dense	inconspicuous
2	15 microns	round	Finely granular	Small, not visible
3	20 microns	Round, oval	Coarsely granular	prominent
4	>20microns	Pleomorphic, lobated	Open, hyperchromatic	macronucleoli

Results

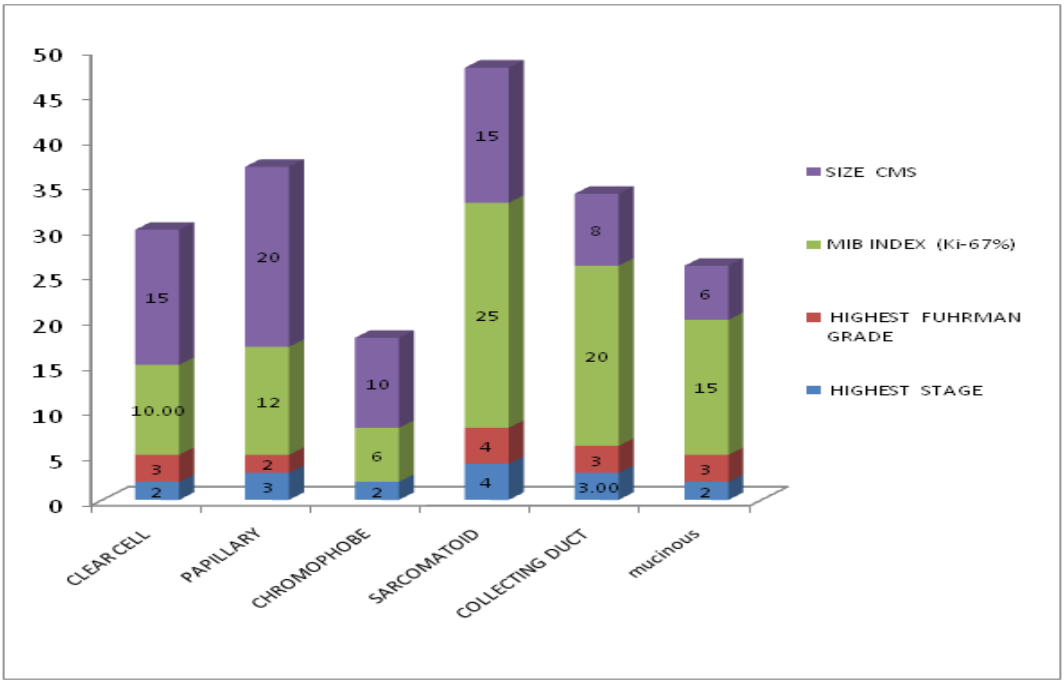
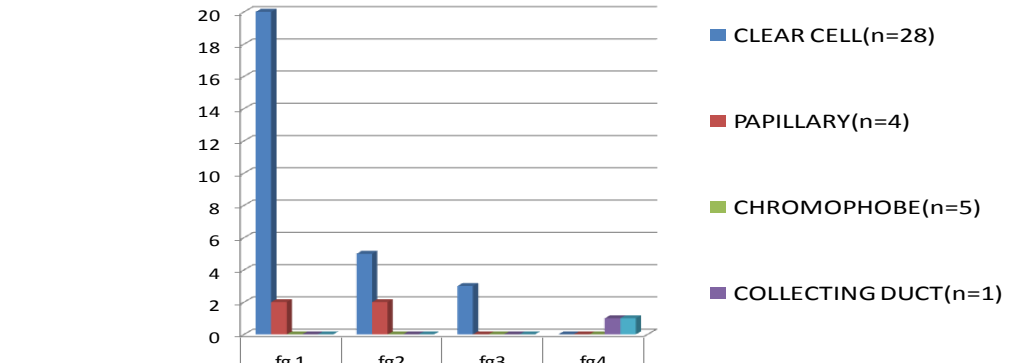


Fig. 1: Types of RCC

Clear cell and papillary tumours are of lower grade with low to moderate MIB index.

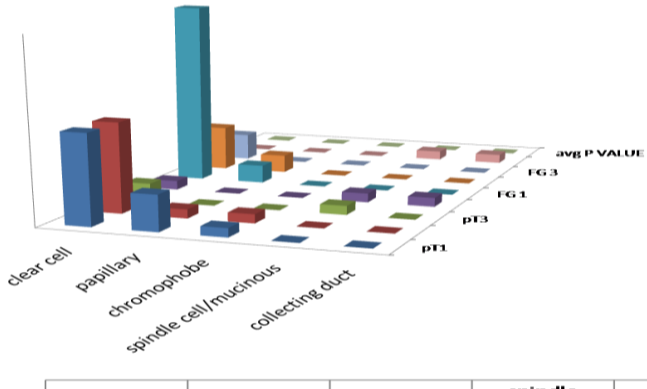
There are 25 Cases with Lymph node involvement in Clear cell variant. Abdominal massin 20%, Flank pain in 33% and hematuriain 40% were expressed as specific symptoms. Hypertension in 53%, Paraneoplastic symptoms in 3%, Cachexia in13%, polycythemia in10% were expressed as non- specific symptoms.

Fuhrman grading of the cases: Clear cell and papillary RCC were of predominantly Fuhrman grade 1 and 2. Fuhrman grade does not apply for Chromophobe RCC. Mucinous, spindle and unclassified type have Fuhrman grade 3 and 4.



	fg 1	fg2	fg3	fg4
CLEAR CELL(n=28)	20	5	3	0
PAPILLARY(n=4)	2	2	0	0
CHROMOPHOBE(n=5)	0	0	0	0
COLLECTING DUCT(n=1)	0	0	0	1
MUCINOUS/SPINDLE(n=2)	0	0	0	1

Fig. 2: Distribution of RCC types



	clear cell	papillary	chromophobe	spindle cell/mucinous	collecting duct
pT1	10	4	1	0	0
pT2	10	1	1	0	0
pT3	2	0	0	1	0
pT4	1	0	0	1	1
FG 1	20	2	0	0	0
FG 2	5	2	0	0	0
FG 3	3	0	0	0	0
FG 4	0	0	0	1	1
avg P VALUE	0.03	0.001	0.003	0.0004	0.001

Fig. 3: Comparison in relation to p value, histological subtype and fuhrman grading

Table 2: The correlation of age, renal vessel and capsular involvement in renal cell carcinomas

Tumour type	Adrenal involvement	Renal vessel involvement (cms)	Gross Capsular Involvement (cms)	Age (mean)
Clear cell	no	0.3 cm in 3 cases None in 25 cases	0.6 cm in 16 cases None in 12 cases	45 yrs
Papillary	no	0.8 cm in 2 cases None in 2 cases	0.4 cms in 2 cases None in 2 case	50 yrs
Chromophobe	no	None in 5 cases	None in 5 cases	40 yrs
Sarcomatoid/ mucinous	no	2 cms in one case	0.7cms in the same case	60 yrs
Collecting duct	no	1.5 cms in one case	0.8 cms in the same case	50 yrs

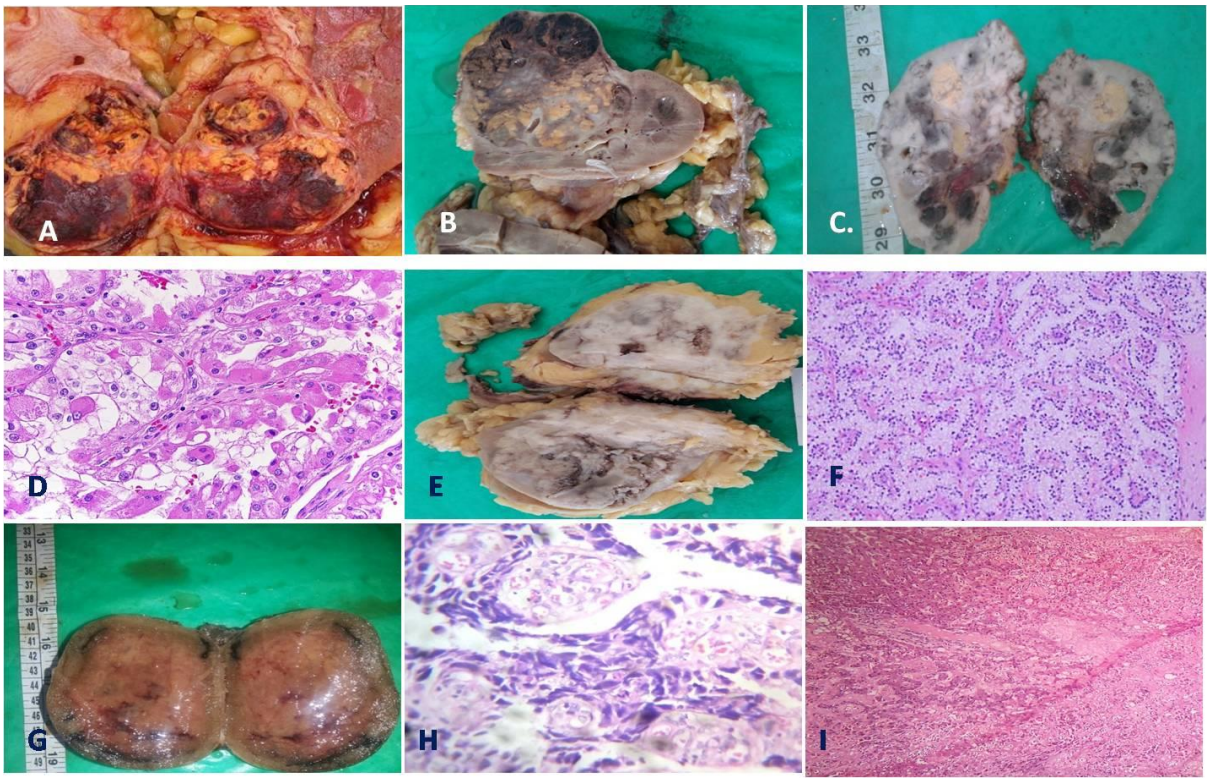


Fig. 4. A. Yellow tan apperence of CCRCC; B. CCRCC.Grey brown tumor tissue with patchy yellow areas; C. CCRCC, oncocytic variant Grossly hemorrhagic foci; D. Clear cells and oncocytic tumor cells (H &E x400); E. Tubulocystic papillary variant Grossly cystic and solid areas F. Tubular formations, papillary foci (H & E x400)G. Chromophobe carcinoma with papillary differentiation. H. Collecting duct carcinoma, I. Chromophobe carcinoma

Discussion

Grossly, most renal cell carcinomas are well delineated and centered on the cortex. Extension to the renal pelvis occurs only late in the course of the disease. In most of these cases there is evidence of polyclonality, suggesting an independent origin. Hemorrhage, necrosis, calcification, and cystic change result in a variegated appearance.[11] Cortical cysts composed of a thick fibrous (often partially calcified) capsule and containing a grumous, yellow, necrotic material represent, in most cases, necrotic renal cell carcinomas.[12] The stroma of renal cell carcinoma is nondescript. A lymphocytic infiltrate is present.

Papillary renal cell carcinoma comprises about 10% of all renal cell carcinomas.[13,14] Microscopically, complex papillary formations are seen, often accompanied by prominent stromal infiltration by neutrophils or foamy macrophages. Psammoma bodies can be seen. The type 1 tumors are accompanied by foamy macrophages and psammoma bodies and are immunoreactive for keratin 7 and MUC1.[15] They also have different cytogenetic abnormalities but their clinical outcome is similar.[16-19]

Although papillary renal cell carcinoma is currently regarded as a distinct subtype, there are solid variants, variants similar to collecting duct carcinoma[20] and variants in which the papillae are lined by oncocytes.

Chromophobe renal cell carcinoma is a well circumscribed, solitary, with a homogeneous gray to brown cut surface devoid of hemorrhage or necrosis,[21] with a characteristic nesting arrangement of the cells, sometimes associated with adenomatous patterns of growth. The tumor cells have sharply defined borders and abundant cytoplasm. The latter has a pale, acidophilic quality, and there is often a clear perinuclear region. These vesicles stain for Hales colloidal iron, indicating the presence of acidic mucins. Calcification is present in nearly half of the cases.[22] Patients with the Birt–Hogg–Dubé syndrome may develop chromophobe renal cell carcinoma and hybrid chromophobe-oncocytic neoplasms.[23,24]

Sarcomatoid renal cell carcinoma makes up about 1% of all renal tumors in adults. It is largely composed of spindle and/or pleomorphic tumor giant cells, and its appearance may simulate malignant fibrous histiocytoma, fibrosarcoma or angiosarcoma. The nuclear grade is usually high.[25,26]

In clear Cell Carcinomas, the cells are large, the appearance of the cytoplasm ranging from optically clear, with sharply outlined boundaries (‘vegetable cells’), to deeply granular forms.[27] The clear cell appearance of the tumor cells results from the

accumulation of glycogen and also of fat, which can be easily demonstrated with PAS and oil red O stains. Cytoplasmic mucin is absent. Tubular, papillary, and cystic formations may be present.

Collecting duct carcinoma constitutes 1–2% of all renal cell carcinomas. It arises from or differentiate toward collecting (Bellini) ducts.[28] The behavior of collecting duct carcinoma is generally very aggressive, many of the patients having distant metastases at the time of presentation.[29]

Tubulocystic carcinoma is a type of renal cell carcinoma with features resembling those of collecting duct carcinoma. Grossly, its appearance has been described as spongy and 'bubble wrap' type.[30]

Mucinous tubular and spindle cell carcinoma (MTSCC) is a newly described type of low-grade renal cell carcinoma. Microscopically, the tumor is composed of large eosinophilic spindle cells separated by a myxoidstroma containing intracellular droplets and surrounded by a component of elongated tubules and papillae covered by bland-looking cuboidal cells.[31]

Cases containing scanty mucin can be misdiagnosed, the presence of a spindle cell component being an important clue for their correct identification. Focal neuroendocrine features have been occasionally found.

Renal medullary carcinoma is centered in the medulla and microscopically exhibits a reticular, yolk sac-like or adenoid cystic appearance, often with poorly differentiated areas in a desmoplasticstroma marginated by lymphocytes.[32]

Renal cell carcinoma with rhabdoid features tumor is quite different from the sarcomatoid renal cell carcinomas. It contains a high-grade component of rhabdoid tumor cells. Like rhabdoid tumors elsewhere, it behaves in a very aggressive fashion.[33]

Most of the initial cases were reported in young people.[58] Papillary structures may be prominent, and the tumor cells can be clear or have a markedly granular eosinophilic cytoplasm.[34]

The Fuhrman system was the most frequently used grading system in RCC but should not be applied for chromophobe RCC. Furthermore, the Fuhrman system has not been validated for most of the new subtypes of renal carcinoma.

For these reasons, the four-tiered WHO/ISUP grading system is recommended by the WHO. For grade 1–3 tumours, the system defines tumour grade based on nucleolar prominence. Grade 4 is defined by the presence of pronounced nuclear pleomorphism, tumour giant cells, and/or rhabdoid and/or sarcomatoid differentiation.[35]

This grading system has been validated for ccRCC and papillary RCC. The VHL tumour suppressor protein pVHL functions as a tumour suppressor via HIF-dependent regulation in most ccRCC. 3 out of 5 researchers, including our study, confirm that Fuhrman Grading can be used as a single independent prognostic predictor for renal cell carcinomas. As once the renal veins and Gerota's fascia are involved then the tumour grade is 4 and pT is 4, then size has no bearing anymore. Involvement of the renal vein, lymph nodes and capsule decreases the positive prognosis for the patient as it increases the grade and stage of the tumour.[36] Oncocytic papillary RCC is temporarily categorised as type 2 PRCC.[37]

The stage, grade, age and calendar year of diagnosis are all important for prognosis. Familial cases are usually bilateral with younger age at presentation with a poor prognosis. Sporadic cases have unilaterality with older age at presentation.[38] This study shows that Fuhrman grade and TNM stage must be correlated with other clinicopathological variables. Renal vessel, Gerota's fascia and lymph node involvement correlates directly with Fuhrman grade. Tobacco smoking has been a well established factor in the causation of RCC. It is an independent prognostic factor in for RCC. Fuhrman system is one of the criteria to determine nucleus diameter.

Conclusion

In the present study, 40 renal cell carcinomas were studied and the clinicomorphological variables were correlated with grading system. The cases of clear cell carcinoma were maximum in number, 28 cases out of 40 cases. 37 were unilateral and 3 were bilateral. FG and TNM staging can be used as single independent prognostic factors. Clear cell and papillary renal cell carcinomas were low grade tumours with pT1-3 and FG I, II. Sarcomatoid and undifferentiated carcinomas were high grade tumours with pT4 and FG IV. There was a strong correlation between pT and Fuhrman grade. There was no positive correlation between necrosis of the tumour and Fuhrman grade, most patients had FG 1 and 2. There was no positive correlation between histological subtype and necrosis. Microvessel involvement and peripelviceal sinus involvement was seen in sarcomatoid variant.

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