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Original Research

Renal Cell Carcinoma- A Morphological Profile

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Abstract
Introduction: *Renal Cell accounts for nearly 3% of all adult malignancies globally and comprises 80-90% of all malignant renal tumors in adult life. The morphological parameters like the histopathologic variant and its nuclear grade determine the aggressiveness of Renal Cell Carcinoma.*
Methods: *49 cases who underwent radical/partial nephrectomy specimens in a tertiary health care centre over a span of 2years were selected. Their gross and microscopic features were studied and results were correlated with the clinical features.*
Results: *Renal cell carcinoma shows varying morphologic features in gross and histologic appearance. The predominant histologic variant is Clear cell variant and predominant nuclear grade of tumours was grade II. There was no correlation between clinical features and grading. Radiological studies have a high sensitivity in detecting Renal cell carcinoma.*
Conclusion: *Thorough evaluation of morphological parameters in Renal Cell Carcinoma is very essential for planning therapy and predicting the disease outcome.*
Keywords: *Kidney, Renal cell carcinoma, Clear cell carcinoma.*

Introduction

What is a human, but an ingenious machine designed to turn with "infinite artfulness, the red wine of shiraz into urine"? So said the storyteller in Isak Dinesen's Seven Gothic tales. The magical organ he described was kidney. This poetically described organ when trapped in the clutches of cancer, becomes an interesting area of study for a pathologist. Renal Cell carcinoma is traditionally known as Grawitz tumour/Hypernephroma/ Renal adenocarcinoma/Granular cell carcinoma of Kidney. It accounts for nearly 3% of all adult malignancies globally and comprises 80-90% of all malignant renal tumors in adult life. This tumor arises from the proximal tubules. About 2,10,000 new Renal cell carcinomas are detected every year and more than 10,000 deaths worldwide annually are contributed by Renal cell carcinoma. Globally there is a trend for a 25% increase in incidence in Renal cell carcinoma including almost all regions and ethnic groups. This global increase in incidence rate may reflect an earlier diagnosis due to widespread use of improved diagnostic imaging techniques such as Ultrasonography, Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI).

Renal cell carcinoma is exclusively a cancer of adults with a peak incidence in the sixth to seventh decades of life and is 2-3 times more common in males than in females. Renal cell carcinoma is rare in the first two decades of life comprising only 2% of peadiatric renal tumors.

Although obesity, smoking and industrial chemical exposure have been implicated as risk factors in the genesis of renal cell carcinomas, the pathogenesis of this tumor is unclear in most cases. Associations of Renal cell carcinoma with Von Hippel Lindau's Disease, Tuberous Sclerosis, Autosomal dominant Polycystic Kidney disease and chronic renal failure have been well documented in literature. Many patients lack the classical clinical trial of renal cancer which comprise haematuria, pain and flank mass.

The clinical course of RCC is notoriously unpredictable with well documented cases of spontaneous regression and metastatic carcinoma in unusual sites. So a thorough evaluation of the known prognostic factors is an essential part in the assessment of patients with RCC, for it is not only critical for the planning of therapy but also important in predicting the disease outcome. Though the stage is the single most predictive factor of outcome of Renal Cell carcinoma, it has been found that RCC in the same stage, particularly stage I, can exhibit different biologic behaviour. This is because various other morphological parameters like the histopathologic variant and its nuclear grade determine the aggressiveness of Renal Cell Carcinoma.

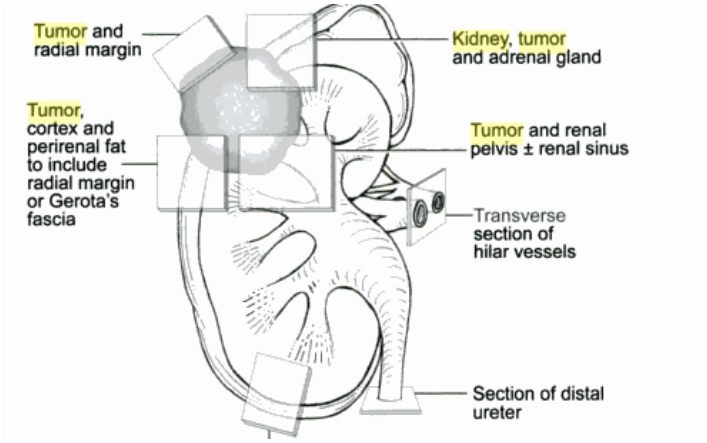
This work is undertaken to study the morphology of renal cell carcinoma by a detailed macroscopic and microscopic analysis. The clinicopathologic correlation of Renal Cell carcinoma is done by collecting detailed clinical history from patients and case records of retrospective cases.

Aims and Objectives

1. To describe morphologic features of classical Renal cell carcinoma and its variants.
2. To analyze the important clinical parameters and to correlate them with grade of Renal cell carcinoma.
3. To study the sensitivity of radiologic study in detecting Renal cell carcinoma.

Materials and Method

The study design was a Descriptive study done in the Pathology Department of a tertiary health care centre in South India. The study duration was 2 years and cases who underwent partial or radical nepherctomy for Renal cell carcinoma were selected for this study. Specimens were weighed, measured and grossed as per recommendations in Rosai Ackerman. The tumor extent, size, location, gross appearance, necrosis, hemorrhage, invasion into capsule, perirenal tissues, calyces, pelvis& renal vein were studied. The kidney was cut sagitally and pelvis, calyces and ureter opened. The capsule was stripped and capsular and perirenal tumor extension were looked for. The specimen was carefully examined for perirenal lymph nodes. Surgically resected margins of ureter were carefully examined. Samples were taken from tumour (minimum of 3 sections including adjacent kidney each of 3 – 5 mm thickness), Pelvis, uninvolved kidney, renal artery, renal vein, ureter (cut end) and lymphnodes. The interface between tumor and perinephric fat was sampled to evaluate perinephric fat invasion.



The H&E stained sections were used for histologic sub typing. Immunohistochemistry was used only to differentiate between sarcomatoid RCC and sarcoma of kidney.

Criteria for Histopathologic Variants (WHO 2004)

Conventional (clear cell) Renal Cell Carcinoma

Clear cell RCC is composed of cells with apically clear cytoplasm arranged in sheets, acini or alveoli with prominent thin walled vasculature, with cells showing distinct cytoplasmic borders and optically clear cytoplasm. Areas of hyalinization, fibrosis, coagulative necrosis may occur. Clear cells may be mixed with cells having eosinophilic cytoplasm. A small proportion of clear cell RCC are cystic (>75% cystic component) and are classified as cystic RCC[1]

Papillary Renal Cell Carcinoma

This variant is composed of fibrovascular cores lined by a single layer of cuboidal cells. The cells may be small with scant cytoplasm or have more abundant eosinophilic cytoplasm with large, nuclei and nucleoli. Papillary RCC can show tubules rather than papillae, lipid laden macro-phages & hemosiderin pigment. Psammomatous calcification and necrosis may be prominent features[2]

Chromophobe Renal Cell Carcinoma

This variant is composed of broad sheets of a mixture of cells with eosinophilic and clear cytoplasm arranged along thin vascular septae. Cell membranes are distinct imparting a "plant like appearance". Anisokaryosis, binucleation, perinuclear halos and irregular nuclei are com-mon. Necrosis and hemorrhage are uncommon[3].

Collecting duct Renal Cell Carcinoma

Collecting duct RCC has varied histologic appearance and is composed of variably sized tubules and papillae lined by cubiodal cells with hob nailing and intervening stroma with inflammation and desmoplasia. Adjacent renal tubules may show dysplastic changes[4].

X p 11 Translocation carcinoma

This tumour is seen in the pediatric age groups and is associated with X p 11.2 translocation. Histologically these tumours show voluminous clear cells arranged in papillae[1].

Renal Cell Carcinoma Unclassified

This category include tumours which cannot be classified into the above described groups. The tumours with extensive necrosis with minimum viable unclassifiable tumor, mucin producing tumors, tumours with sarcomatoid change with unclassifiable epithelial elements comes under this group.

Sarcomatoid RCC: Rather than a separate variant, it is a change which can occur in all subtypes of RCC. It is defined as a high grade spindle cell malignancy exhibiting morphologic or immunohistochemical evidence of epithelial origin and composed of pleomorphic spindle cells with heterologous elements[5,6]

Nuclear grading is done by Fuhrman grading system by light microscopy. This was a four grade system based on the nuclear size, shape, contour and conspicuousness of nucleoli and its size and the magnification at which it could be observed.

Fuhrman grading system was defined as follows :

Grade I- Tumors composed of cells with small (10micron meter) round nuclei with inconspicuous or absent nucleoli.

Grade II- Tumors with larger nuclei (15 micron meter) with irregular out lines and with evident nucleoli.

Grade III- Tumours with larger nucleoli approximately 20 micron meter with an obvious irregular outline and large nucleoli.

Grade IV -Tumors resembling Grade III but with bizarre multilobated nuclei and heavy chromatin clumps.

Results

During this study period 49 cases of Nephrectomy specimens diagnosed as Renal Cell Carcinoma were received. Among 49 cases, 47 were Radical Nephrectomy specimens and 2 were partial nephrectomy specimens.

The age of patients ranged from 20-70 years eldest being 70years and youngest was a 21 year old. The age distribution of patients are given in table 1

Age	No:of patients	Percentage
20-29	1	2.04%
30-39	7	14.2%
40-49	14	28.5%
50-59	16	32.6%
60-69	9	18.3%
70-79	2	4.08%
Total	49	100%

There was male predominance in the study, males constituted 31 cases and females 18 cases. The male to female ratio was 1.7: 1

The gross and microscopic morphology of tumors were studied and analyzed The location of tumor and weight of nephrectomy specimens were studied and analyzed. In 28 cases tumor was located in Right kidney and in 21 cases tumor was located in left kidney.

Based on the location of tumor in kidney the tumor were grouped into upper pole, middle pole and lower pole tumors. 25 cases (51.02%) were upper pole followed by 15 cases (30.6%) in the lower pole of kidney. 5 cases showed tumor involvement of entire parenchyma and 4 cases were located in inter polar area. All nephrectomy specimens were weighed. Majority of nephre-ctomy specimens 26(53.06%) weighed between 500gm to 1000gm. 16 cases including the partial nephrectomy specimens weighed less than 500gm. The dimension of tumours were measured. Based on the longest dimension the tumors were grouped into 3. Those that measured between 0-4cm as small, 5-10cm as medium and more than 10cm were grouped as large tumors. In this study majority of tumors, 28 (57.14%) were medium sized followed by large tumors (26.5%).

The histomorphology study using H & E stained sections was done. This included the predominant pattern of arrangement of tumor cells, cell features and nuclear grading. Most of the tumors showed mixed patterns and mixed cytologic features, But the predominant patterns and cytologic features which constituted 75% of the tumours was taken into account.

The predominant architectural pattern observed in 49 cases was solid 22 (44.8%) followed by Tubular patterns 11 (22.4%).

The cell type was classified based on cytoplasmic characteristics. The predominant cell type which constitute 75% of tumor was used for classifying the tumors. 8-10 number of slides were studied per case.

The cells with clear cytoplasm, abundant granular cytoplasm, spindle cells were the 3 major cell types observed in the study. The majority of tumours showed mixed clear and granular ce

As per WHO classification of Renal tumors the cases were classified into different histologic variants. The architectural patterns, cytologic features, stromal features were the criteria used for classifying tumors. The predominant variant in the current study was clear cells (33 (67.3%)) followed by sarcomatoid 16.3%. The tumors were staged based on perinephric fat invasion, LN metastasis, vascular invasion and distant metastasis. The stage was not assessed in 2 partial nephretomy specimens. Majority of cases had stage 1 disease 63.8%).

Distribution of patients in various stages in relation to the tumor Size

Stage 1 and stage 2 diseases were distributed mainly in small and medium categories. Stage 4 disease has one case with small sized tumor.

Table 02

Tumor size	Stage				Total no: of patient in each tumor category
	I	II	III	IV	
Small	5	0	0	1	6
Medium	18	4	4	2	28
Large	7	2	2	2	13

Distribution of patients in various nuclear grades in relation to tumor stage was also analyzed.

One most important observation in this study was increased incidence of perinephric fat, blood vessel, lymphnode invasion in grade 4 tumours. The distribution of patients according to grade and stage is given in table -3.

	Grade			
Parameters	I	II	III	IV
Perinephricfat Invasion	0	6	4	4
Blood vessel	0	0	1	2
Lymphnode Invasion	1	0	0	1

The clinical presentations of patients were analyzed. Majority of patients presented with Flank mass, 20 cases (40.8%), followed by Hematuria (18.3%) of cases. The patients who presented with metastic lung disease were 2 in number and one patient presented with Hemiplegia due to metastatis to brain. The distribution of patients according to clinical symptoms is given in Table-4.

Symptoms	No: of patients	Percentage (%)
Flank mass	20	40.8%
Hematuria	9	18.3%
Abdominal pain	8	16.3%
Incidental	6	12.2%
Fever	2	4.08%
Metastatis to lung	2	4.08%
Fatigue	1	2.04%
Hemiplegia	1	2.04%
Total	49	100%

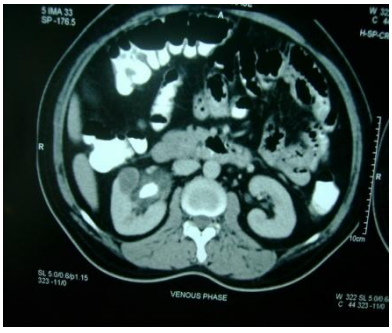
The radiologic correlation was assessed based on the CT diagnosis. 90% cases had a radiologic diagnosis of RCC, but a few cases had a false radiologic diagnosis as benign and metastatic lesions. Table 5

Radiologically cancer	Histologically cancer	Histologically no cancer
Positive	47 true positive	0 false positive
Negative	2 false negative	0 true negative
total	49	0

Sensitivity =95.9% Percentage of false negatives =4.08%

Figure 1 A

Figure 1B

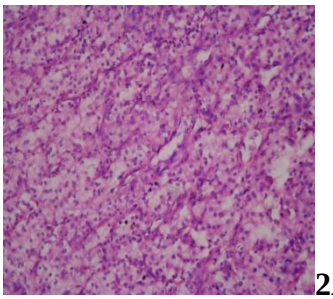


1 A-Macroscopy- Radical Nephrectomy specimen showing tumor located in the inter polar region.

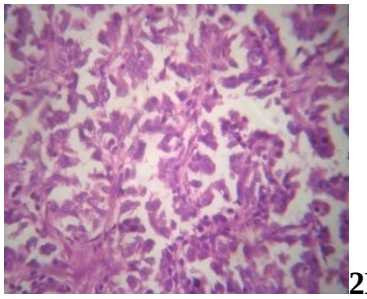
1B- CT image of a Renal cell carcinoma case

Figure 2

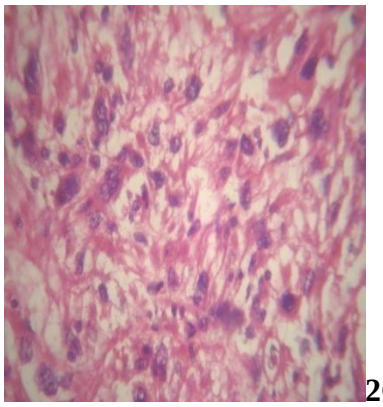
Microscopic Grades Of Renal Cell Carcinoma



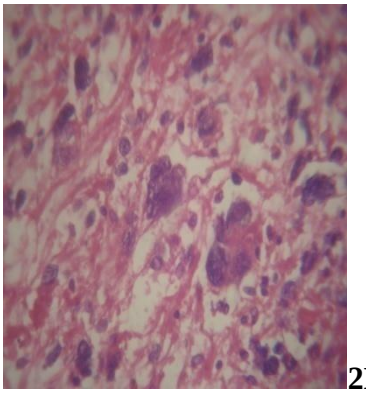
2A- Grade I



2B Grade Ii



2C Grade Iii



2D Grade Iv

Discussion

Renal cell carcinoma, well known for its unpredictable out comes, was studied to analyze its morphological features and was correlated with

clinical and radiologic pictures in the current study.

In the present study majority of patients were in the 5th to 6th decade. The present study is in concordance with study done by Aron and Gross in (1969[7]) in which peak age of incidence is reported as 5th and 6 th decade.

In this study males were 1.7 times more frequently affected than females. The tumor occurs more frequently in males than females with varying ratio in different reports ;2: 1male to female ratio observed in study by Riches, Grffiths and Thackray in 1951 and 2.6 M: 1 F ratio in Dianna sike et al study 2006. These studies also establish male predominance in Renal cell carcinoma occurance[8]

The current study showed predominance of Right sided tumor over left sided tumors. Riches et al study in 1951[7] establishes equal frequency of occurrence in each kidney.

The predominant location of tumor on kidneys was upper pole . But as per Riches, Griffiths and Thackray 1951[7] there is no predilection for any renal segments for tumor

Majority of Nephrectomy specimens with tumor weighed between 500- 1000g with tumor sizes varying between 5-10cm.Tumor size ranged from few millimeters to huge sizes filling entire abdomen in the morphologic study conducted by Farrow in 1997[9] and in this study larger tumor sizes was associated with local extension, vascular invasion and metastasis. Medeiros et al[10] study showed tumor size greater than 10 cm was associated with poor prognosis, and small sized tumor <5 cm was associated with good prognosis than medium sized tumors which measured between 5-10 cm. In the present study medium sized tumors predominated and were distributed in all stages with largest number of cases in stage I. But large tumors also had maximal distribution in stage I disease. This observation is in concordance with the study by Bretheau et al[11], which also showed majority by small and medium sized tumors in stage I.

Histology of tumors showed more than one architectural pattern ; the predominance was for solid pattern followed by tubular and papillary pattern. This observation is similar to the study by Mancille Jimnize al in 1998[12]

The predominant cell type in tumor was clear cell type. In Murphy and Mostofi (1965)[13] series show mixed cell patterns as the predominant cell type

Clear cell variant was the predominant variant in all histologic subtypes , followed by sarcomatoid variant. A few cases of collecting duct carcinoma and oncocytic variant was also present. The frequency of histologic variants is similar to the observations of John.c.Cheville et al study of 2003 ,Frank et al study of 2002,and Moch et al of 1994[14].

The Fuhrman et al grading system was used for grading. The predominant grade in current series is grade II with minority of cases under grade III &IV and least number of cases in grade I. The distribution of patients in the different grade groups appeared similar to study by Medeiros et al and Bretheau et al studies [10,11]

Reference	Grade I	Grade II	Grade III	Grade IV
Mederios et al	7.4%	33.2%	37.2%	21.6%
Bretheau et al	28%	31%	31%	10%
Present study	4.08%	48.9%	26.5%	20.4%

One interesting finding in this study is the higher incidence of perinephric fat invasion, blood vessel invasion and lymphnode invasion in grade IV tumors. This observation is similar to the aggressiveness of grade IV and III tumors with decreased survival rates as observed in Medeiros et al and Bretheau et al studies[10,11]

In the current study sensitivity of radiologic investigations to detect renal cell carcinoma is 95.8% and the percentage of false positives is 4.08 %.This establishes radiology as an invaluable aid in the diagnosis of renal cell cancer. The study is comparable with the observations by Motzer et al (1999) in which radiologic sensitivity was observed as 93%[15] of cases

Conclusions

- Renal cell carcinoma shows varying morphologic features in gross and histologic appearance.
- The predominant nuclear grade of tumours was grade II. There was no correlation between clinical features and grading.
- Radiological studies have a high sensitivity in detecting Renal cell carcinoma

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