

# Morphological Variants of Renal Carcinoma in Radical Nephrectomy Specimens

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## ABSTRACT

**Objective:** To determine the morphological variants of Renal Cell Carcinoma (RCC) to detect the commonest histopathological type with special focus to the newly introduced entity Clear Cell Papillary Renal Cell Carcinoma (CCPRCC).

**Study Design:** Case series.

**Place and Duration of Study:** Department of Pathology, Basic Medical Sciences Institute, JPMC, Karachi, from January 2007 to December 2012.

**Methodology:** Paraffin embedded blocks of 32 cases of radical nephrectomy specimens for renal mass were selected from records of Pathology Department, BMSI. Cases were excluded due to inadequate biopsies. Remaining 30 cases of renal cell carcinoma were included in study. H & E staining was done for all cases and PAS stain was employed for a few cases. All cases were reviewed under light microscope.

**Results:** The 30 cases of renal cell carcinoma included 21 (70%) clear cell renal cell carcinoma, 03 (10%) clear cell papillary renal cell carcinoma, 02 (6.6%) papillary renal cell carcinoma and 04 (13.33%) hybrid tumors. Majority of cases (53.3%) found in age range between 40 - 60 years while 23.33% cases were found in 7th and 6.6% in 8th decade of life. While 16.66% cases were in younger age group that is between 31 - 40 years of age. Sixty percent cases of right radical nephrectomies and 40% cases of left radical nephrectomies.

**Conclusion:** CCRCC was most common histopathologic type followed by CCPRCC, hybrid tumors and PRCC.

**Key Words:** RCC (Renal Cell Carcinoma). CCRCC (Clear Cell Renal Cell Carcinoma). CCPRCC (Clear Cell Papillary Renal Cell Carcinoma). PRCC (Papillary RCC). VHL (Von Hippel Lindau) gene.

## INTRODUCTION

Renal cell carcinoma also known as hypernephroma is the most common adult renal epithelial carcinoma that originates from the lining of the proximal convoluted tubules and accounts for more than 90% of all renal malignancies.<sup>1,2</sup> Cigarette smoking, trichloroethylene exposure, obesity, hypertension, dietary, environmental, and hormonal factors are most common risk factors which have been implicated in development of RCC;<sup>3</sup> hysterectomy and injury to ureter during surgery in a female patients produce a double risk.<sup>3</sup> The incidence of RCC is increasing yearly in Pakistan and worldwide. National cancer institute shows 64,770 new cases and 13,570 deaths from kidney (renal cell and renal pelvis cancers) in United States of America in 2012.<sup>4</sup> Kidney cancer incidence statistics (2009) shows kidney cancer to be the eighth most common cancer in the United Kingdom, accounting for around 3% of all new cases in England, Wales, Scotland, Northern Ireland.<sup>5</sup>

Cancer profile of Hyderabad, Pakistan, 1998 - 2002 shows the incidence of 1.8/100,000 RCC.<sup>6</sup> Annual

cancer registry report of Shaukat Khanam Memorial Cancer Hospital (2011) showed 100 case of kidney tumors in 4537 malignant cases.<sup>7</sup> The tumor registry of Armed Forces Institute of Pathology, Rawalpindi, from 2005-2008 showed 236 diagnosed renal tumors.<sup>8</sup> SIUT preliminary report of period from April to October 2004 shows 50 patients of RCC.<sup>9</sup> Clear cell renal cell carcinoma is commonest histological type representing 70% of RCC while papillary renal cell carcinoma accounts 10 - 15%, chromophobe RCC 5% and other types of RCC in small numbers. The usual age at diagnosis is 50 - 60 years, Rarely RCC occurs in children. Male/female ratio is 2:1 and incidence of bilaterally is less than 1%.<sup>2,3,8,10,14</sup>

Previously some RCC were morphologically reported as mixed variant. Recently, the new entity Clear Cell Papillary Renal Cell Carcinoma (CCPRCC) has been introduced to describe RCC with clear cell and papillary patterns. While term of hybrid tumors is being used where multiple histopathologic variants of RCC are present in a single case.<sup>15-20</sup>

The present study was aimed at reviewing the cases of RCC particularly those previously reported as mixed variant RCC in order to identify newly defined CCPRCC.

## METHODOLOGY

The present study was based on the morphological review of radical nephrectomy specimens for renal

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*Received: July 23, 2013; Accepted: July 11, 2015.*

masses diagnosed as renal cell carcinoma, from January 2007 to December 2012 at BMSI, JPMC, Karachi. Two cases were excluded due to inadequate biopsy specimen. Eventually selected cases underwent detailed morphological review under light microscope.

Heamatoxylin and Eosin staining were done for all cases and PAS staining was done for a few cases.

Sections were processed with Xylene-1 for 10 minutes, Xylene-2 for 10 minutes, absolute alcohol for 5 minutes, 95% alcohol for 5 minutes, 80% alcohol for 5 minutes, 70% alcohol for 5 minutes, rinsed in tap water for 2 minutes, Harris hematoxylin for 5 - 10 minutes with, acid alcohol 1%, 3 - 5 dips and then washed in tap water. Ammonia water 3 - 5 quick dips were given and then the specimens were rinsed in tap water for 10 - 15 minutes, Eosin for 2 minutes, 70% alcohol (5 quick dips), 80% alcohol (5 quick dips), 95% alcohol (5 quick dips), absolute alcohol two changes (5 quick dips), Xylene-2 changes for 5 minutes each and then mounted in DPX.

The data feeding and analysis was done on computer package SPSS (Statistical Packages of Social Sciences) version 16.0. Clinical characteristics were summarized in terms of frequencies and percentages for qualitative variables (gender, age grouping, site of renal nephrectomy specimens, morphological type) and mean  $\pm$  SD was determined for age in year.

## RESULTS

Total numbers of 352 renal surgical pathology cases were registered in Pathology Department, BMSI, JPMC from 1st January 2007 to 31st December 2012. Out of these 274 (77.84%) were biopsies, 48 (13.63%) were nephrectomies and 30 (8.5%) were radical nephrectomies done for renal neoplasm.

There were 18 (60%) cases of right radical nephrectomies and 12 (40%) of left radical nephrectomies, 12 male and 06 female patients for right side renal mass and 08 males and 04 females for left kidney tumor.

All the radical nephrectomy specimens received were diagnosed as renal cell carcinoma. These included clear cell carcinoma 21 (70%), clear cell papillary renal cell carcinoma 03 (10%), papillary cell carcinoma 02 (6.66%) and 04 (13.33%) hybrid cases (Table I).

Table II shows the vascular invasion of tumor in 04/21 (19.04%) case of clear cell carcinoma and 01/4 (25%) hybrid tumor (Figure 1 - 3). The capsular invasion was seen in 08/21 (38.09%) CCRCC 01/3 (33.3%) CCPRCC and 01/4 (25%) hybrid tumor, necrosis seen in 09/21 (42.8%) case of CCRCC, 01/3 (33.3%) CCPRCC and 01/2 (50%) papillary RCC. Perinephric fat involvement seen in a single case of CCRCC (4.76%). Only one case of clear cell carcinoma received with single lymph node which was negative for tumor metastasis.

Table III shows the distribution of RCC according to age and gender 20 male patients and 10 female patients, male /female ratio is 2:1, 5 cases in 4th, 8 cases in 5th, 8 cases in 6th, 7 cases in 7th and 2 cases in 8th decade of life.

The distribution of different morphological variants of renal cell carcinoma according to the age shown in Table IV, 03 (14.28%) in 4th, 5 (23.8%) in 5th, 7 (33.33%) in 6th, 4 (19.04%) in 7th and 2 (9.5%) in 8th decade of life respectively including 16 male and 5 female patients. CCPRCC with one case each (33.33%) in 5th, 6th and 7th decades of life respectively including one female and two male patients. Four hybrid cases with frequency of 2 (50%) in 4th decade, one (25%) each in 5th decade and in 7th decade of life.

**Table I:** Distribution of various morphological types of RCC amongst 30 cases of radical nephrectomies.

Morphological types	No of cases	%
Clear cell carcinoma	21	70%
Clear cell papillary RCC	3	10%
Papillary RCC	2	6.66%
Hybrid tumor	4	13.33%
Chromophobe tumor	0	0
Total	30	100%

**Table II:** Distribution of case according to vascular invasion, capsular invasion, necrosis, perinephric fat involvement (n=30).

Morphological types	Vascular invasion	Capsular invasion	Necrosis	Perinephric fat involvement
CCRCC	4/21 (19.04%)	8/21 (38.09%)	9/21 (42.8%)	1/21 (4.76%)
CCPRCC	0	1/3 (33.3%)	1/3 (33.3%)	0
PRCC	0	0	1/2 (50%)	0
Hybrid tumor	1/4 (25%)	1/4 (25%)	0	0

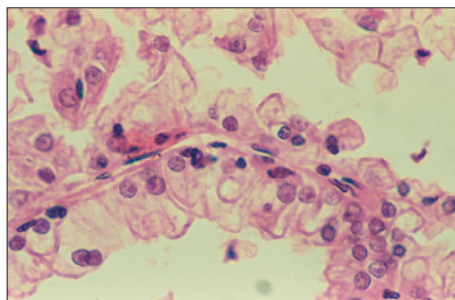
**Table III:** Distribution of RCC according to age and gender (n=30).

Age group (years)	No. of cases	Gender	
		Male	Female
10 - 20	Nil	Nil	Nil
21 - 30	Nil	Nil	Nil
31 - 40	5	2	3
41 - 50	8	4	4
51 - 60	8	6	2
61 - 70	7	6	1
71 - 80	2	2	0

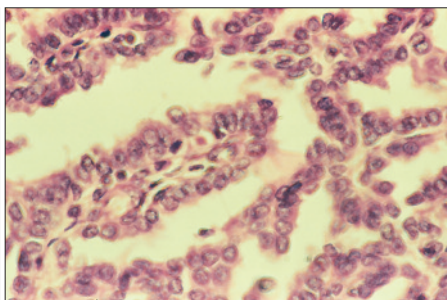
Male to female ratio: 2:1

**Table IV:** Distribution of RCC according to age groups (n= 30).

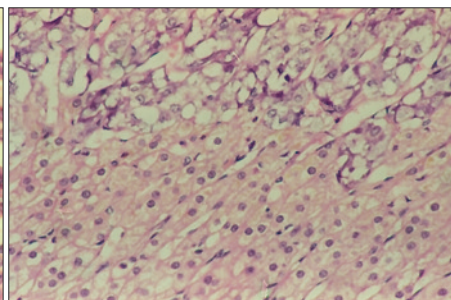
Age group (years)	CCRCC	CCPRCC	PRCC	Hybrid tumor	(%)
10 - 20	nil	nil	nil	nil	-
21 - 30	nil	nil	nil	nil	-
31 - 40	3	-	-	2	16.66%
41 - 50	5	1	1	1	26.6%
51 - 60	7	1	-	-	26.6%
61 - 70	4	1	1	1	23.33%
71 - 80	2	-	-	-	6.6%



**Figure 1:** Photomicrograph of clear cell papillary renal cell carcinoma (40 x).



**Figure 2:** Photomicrograph of papillary renal cell carcinoma (40 x).



**Figure 3:** Photomicrograph of hybrid tumor (20 x).

## DISCUSSION

The objective of the present study was morphological evaluation of RCC in accordance with the new categories of classification. In this study RCC is 8.5% of total renal pathologies received in BMSI, JPMC during 2007 - 2012. Agha *et al.* shows 12.4% of renal cell carcinoma and study from Latif *et al.* shows 14.36% of RCC during 1987 - 1997 in SIUT, Karachi.<sup>9,10</sup> These findings are higher mostly due to large sample size and increased study duration.

In present study 60% cases (12 male and 6 female patients) showed right sided RCC while 40% cases (8 male and 4 female patients) were with left side RCC. Eggenger *et al.*<sup>11</sup> showed 54.6% in right kidney and 45.4% in left kidney cases, however, Latif *et al.*<sup>9</sup> showed more in left kidney than the right. This could be an incidental finding because no emphasis on laterality could be found in any other studies.

Among the various morphological types; clear cell carcinoma was diagnosed in 70% of cases. It is the commonest histological type revealing sheets, acini and alveolar pattern of clear cells with eccentric nuclei. At places, granular appearance and distinct cell margins along with Furhmans nuclear grade-2 also seen. Mohsin *et al.*<sup>12</sup> showed 68.5% of CCRCC, Prasad *et al.*<sup>3</sup> also reported clear cell carcinoma as 70% of total RCC, Latif *et al.*<sup>9</sup> shows 73.2% CCRCC, Moatasim<sup>13</sup> shows 69.2% CCRCC. Khadim *et al.*<sup>8</sup> shows 73% CCRCC. The predominant morphological pattern in present study is in close approximation with the above mentioned studies.

Clear cell papillary renal cell carcinoma is a newly introduced entity revealing large clear cells arranged in papillary pattern separated by thin fibrous septae was found in 3 cases of our series. Previously these cases were diagnosed as mixed variant of RCC with Furhmans grading 1 - 2. Park *et al.*<sup>14</sup> shows 2.9% of CCPRCC in their study which is lower than that found in this study. Sinnot<sup>15</sup> and Bing<sup>16</sup> have defined the confusing situation of morphological type of CCPRCC as clear cell carcinoma or papillary carcinoma but no confusion regarding the frequency of these morphological types. The reason for a higher frequency in present study is the use of strict morphological criteria in separating the variant form from CCRCC. Three cases of CCPRCC in

this study were seen between age group 50 - 65 years in 02 males and 01 female patient. Gobbo *et al.* has also reported CCRCC in age range between 53 - 64 years including 03 males and 02 females. Gobbo *et al.*<sup>22</sup> also reports CCPRCC as having a distant molecular genetic profiles.

Two cases (6.6%) diagnosed as papillary RCC showed small cells arranged in papillary pattern with Furhmans nuclear grade-1. Both the cases were type-1 papillary carcinoma; this was comparable with the study by Khadim *et al.*<sup>8</sup> who showed 6.77% of PRCC, Mohsin *et al.*<sup>12</sup> showed 9% PRCC, Ross *et al.*<sup>17</sup> showed 11 - 20%, Latif *et al.*<sup>9</sup> showed 14.6% and Prasad *et al.*<sup>3</sup> showed 10 - 15% of PRCC. The variation in the findings is most probably due to difference in sample size.

The present authors found 13.33% (04) hybrid tumors in this study amongst which 3 cases were combination of foci of clear cell, papillary pattern and oncocytic pattern with Furhmans nuclear grade-2. While one case showed the clear cell foci in combination with papillary arrangement and focal chromophobe pattern with Furhmans nuclear grade-3. Tait *et al.*<sup>18</sup> all showed a combined finding of tumor with clear cell and papillary arrangement. Adley *et al.*<sup>19</sup> showed the different kind of RCC including clear cell, oncocytic and chromophobe pattern in all hybrid tumor.

Amongst these cases the chromophobe RCC was found only as hybrid tumors despite the fact that suspicious cases were processed with Hale colloidal iron stain. Khadim *et al.*,<sup>8</sup> Latif *et al.*<sup>9</sup> and Moatasim<sup>13</sup> have also described the chromophobe carcinoma as a rare finding.

The size of tumor, vascular invasion, capsular invasion and perinephric fat involvement were looked for in these cases. The largest tumor was 12 x 12 cm and smallest was 3 x 2 cm. Latif *et al.*<sup>9</sup> showed maximum size of tumor as 18 cm and smallest size as 3 cm, Moatasim<sup>13</sup> reports a range between 2.8 - 9 cm of tumor size.

In this series vascular invasion seen in 16.6% out of 30 cases. Agha *et al.*<sup>10</sup> found 16.25% cases with vascular invasion which almost matched with the present findings.

Capsular invasion was seen in 33.3% cases in this series which is in close proximity with findings of Prasad *et al.*<sup>3</sup> showing 45% of vascular or capsular invasion.

Here, 36.66% cases had necrosis and 4 cases out of total RCC were finally diagnosed with vascular invasion, capsular invasion and necrosis. Single case with perinephric fat infiltration was also found. According to Volpe and Patard<sup>20</sup> necrosis is a bad prognostic factor. Renal vein involvement alone has a good prognosis with better survival rate of patients but worst prognosis along with perinephric fat invasion.

In this study majority of cases (53.3%) were found in age range between 40 - 60 years while only 23.33% cases were found in 7th decade and 6.6% cases in 8th decade. These findings are comparable with Khadim *et al.*<sup>8</sup> and Walsh and Campbell urology<sup>2</sup> reporting the average age of diagnosis from 55 - 60 years with male predominance and common in 6th to 7th decade of life, Agha *et al.*<sup>10</sup> showed 74% of case between 40 - 60 years of age, Taccoen<sup>21</sup> shows 92.4% patients with more than 40 years of age.

Approximately 16.66% of these cases were in younger age group that is between 31 - 40 years of age which is in contrast with Mohsin *et al.*<sup>12</sup> showing 9% of renal tumors were either 40 years or less and Taccoen<sup>21</sup> showing 7.5% of less than 40 years. The older age group may fall into sporadic group and younger age group warrants the need for VHL mutations evaluation to differentiate hereditary type from sporadic cases. One of the reasons that this study showed a higher figure of younger age group could be due to the lack of awareness regarding exact age, as most of the cases were from lower socioeconomic and uneducated back-ground.

The limitation of the study was lack of IHC facility in our Institution, which was overcome by using strict morphological criteria and morphology was to be conspicuous with the diagnostic difficulty. Hence, the need of immunohistochemistry was not felt. Further studies including molecular profile are recommended to help identify this unusual tumor presenting diagnostic dilemma for histopathologist particularly in public sector hospitals where the costly ancillary techniques such as immunohistochemistry and polymerase chain reaction are not available.

## CONCLUSION

The present study shows 10% frequency of clear cell papillary renal cell carcinoma.

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