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Renal Cell Carcinomas in Ibadan; A Further Histopathological Study

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Abstract

Background: Renal cell carcinoma (RCC) is the most lethal urological cancer accounting for about 2% of all cancer deaths worldwide. It is relatively rare in Africans but contributes to significant morbidity and mortality from cancers of the urogenital tract. A previous study of RCC in Ibadan is succeeded by this current review

Materials and Methods: The bio-data of all the patients with histologically diagnosed renal cell carcinoma was obtained from the surgical daybook of the Department of Pathology, UCH, Ibadan within the study period (January 2007 to December 2016). H&E stained tissue slides of all cases of renal cell carcinomas seen in the surgical daybook were reviewed for confirmation of the histological diagnosis of renal cell carcinoma. The morphological patterns and Fuhrman grading were determined for all the cases of clear cell and papillary renal cell carcinomas while a novel tumour grading adapted for chromophobe renal cell carcinomas was used to grade all 3 cases of Chromophobe RCC seen in this study. Frequency statistics and chi-square were applied on data to determine proportions and associations using Statistical Package for Social Sciences (SPSS) version 23.

Results: A total of 48 cases of renal cell carcinomas were seen within the study period that met the inclusion criteria for the study. Clear cell RCC was the commonest variant and comprised 30 cases (62.5%) followed by 14 cases of papillary RCC (29.17%) while 3 cases of Chromophobe renal cell carcinoma was seen comprising 6.25%. Only one unclassified variant was seen making up 2.08%. The age range of the patients was between 3 to 76 years with an average age of 44.17years. The male to female ratio was 1:1.3. Grade 2 nuclei were predominant (43.75%) while Grade 4 nuclei had the lowest frequency (6.25%). The association between the morphological patterns and the nuclear grading was however not statistically significant.

Conclusion: This study demonstrated that the clear cell variant of RCC was the commonest morphological pattern seen in our environment with most of our cohort having low grade nuclei which appears different from the findings of the previous study but correlates well with the global trends in RCC. The nuclear grading as prognostic marker also appears favourable. A further study of the molecular genetics of this cancer will help to determine whether this cancer is mainly familial or sporadic.

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Abstrait

Contexte: Le carcinome à cellules rénales (RCC) est le cancer urologique le plus mortel, responsable d'environ 2% de tous les décès par cancer dans le monde. Il est relativement rare chez les Africains mais contribue à une morbidité et une mortalité importantes par cancers du tractus urogénital. Une étude précédente du RCC à Ibadan est remplacée par cette revue actuelle.

Matériels et méthodes: Les données biographiques de tous les patients atteints d'un carcinome à cellules rénales diagnostiqué histologiquement ont été obtenues à partir du journal chirurgical du Département de pathologie, UCH, Ibadan au cours de la période d'étude (janvier 2007 à décembre 2016). Des lames de tissu colorées à l'H&E de tous les cas de carcinomes à cellules rénales observés dans le journal chirurgical ont été examinées pour confirmer le diagnostic histologique de carcinome à cellules rénales. Les schémas morphologiques et le classement de Fuhrman ont été déterminés pour tous les cas de carcinomes rénaux à cellules claires et papillaires, tandis qu'un nouveau classement tumoral adapté aux carcinomes rénaux chromophobes a été utilisé pour classer les 3 cas de RCC chromophobe observés dans cette étude. Les statistiques de fréquence et le chi carré ont été appliqués aux données pour déterminer les proportions et les associations à l'aide de la version 23 du package statistique pour les sciences sociales (SPSS).

Résultats: Au total, 48 cas de carcinomes à cellules rénales ont été observés au cours de la période d'étude et répondaient aux critères d'inclusion de l'étude. Le RCC à cellules claires était la variante la plus courante et comprenait 30 cas (62.5%) suivis de 14 cas de RCC papillaire (29.17%) tandis que 3 cas de carcinome à cellules rénales chromophobes représentaient 6.25%. Une seule variante non classée a été observée, représentant 2.08%. La tranche d'âge des patients était comprise entre 3 et 76 ans avec un âge moyen de 44.17 ans. Le ratio hommes/

femmes était de 1:1.3. Les noyaux de grade 2 étaient prédominants (43.75%) tandis que les noyaux de grade 4 avaient la fréquence la plus faible (6.25%). L'association entre les patrons morphologiques et le classement nucléaire n'était cependant pas statistiquement significative.

Conclusion: Cette étude a démontré que la variante à cellules claires du RCC était le modèle morphologique le plus courant observé dans notre environnement, la plupart de notre cohorte ayant des noyaux de bas grade, ce qui semble différent des résultats de l'étude précédente, mais correspond bien aux tendances mondiales du RCC. Le classement nucléaire comme marqueur pronostique apparaît également favorable. Une étude plus approfondie de la génétique moléculaire de ce cancer permettra de déterminer si ce cancer est principalement familial ou sporadique.

Introduction

Renal cell carcinoma(RCC) is the 3rd most common cancer of the genitourinary tract and the most lethal urological cancer accounting for approximately 2% of all cancer deaths worldwide.[1] Globally, RCC accounts for about 3% of all adult cancers while in Nigeria, it accounts for between 0.3% and 2.3%.[2] The incidence rate for RCC is low in developing countries and in Nigeria particularly, it is relatively low with an estimated incidence rate of 0.3 to 0.6 per 100,000 populations[2,3] compared to the standardized incidence rate of RCC in the world estimated at 4.4/100,000 population people; 6/100,000 population in men, and 3/100,000 population in women.[4]

RCC represents a heterogeneous group of cancers arising from renal tubular epithelial cells with the most common subtypes of RCC being clear cell RCC (ccRCC), papillary RCC, and chromophobe RCC.[5] Approximately one-third of the patients with renal cell carcinoma will present with metastasis and many patients will develop metastasis after surgical resection.[1,6] The outlook for patients with distant metastases is poor, with a 5-year survival rate of less than 10% for patients presenting with stage IV disease.[7] There has been tremendous development in effective molecular targeted therapies in the past few years for specific types of renal cell carcinoma with well-defined histological and molecular abnormalities; therefore accurate histological diagnosis and classification is increasingly important.[1]

Renal cell carcinoma (RCC) is a rare cancer in developing countries like Nigeria. However, with an increasing understanding of its epidemiology, the increasing availability of trained personnel, improvement in diagnostic facilities, and greater awareness in the populace, an increase in its incidence as was witnessed in developed nations in the last few decades could be safely predicted.[8] The mortality rate appears to be high in Nigeria ranging from 40.9 to over 90%.[9,10] Africa has the lowest cumulative risk of incidence and mortality from RCC, put at below 0.2% for both sexes with the highest estimated mortality rates being reported in Egypt (2.4), Libya (2.3), Mali (1.8), and Tunisia (1.7), all per 100,000 population and with a cumulative mortality risk between 0.17% and 0.27%.[11] A previous similar study from the same institution by Odubanjo et al showed that renal cell carcinoma in Ibadan occurs two decades earlier than in Caucasians and papillary RCC was the most common histological subtype in Ibadan.

This study therefore sought to update the morphological patterns of RCC in our environment after the last review, since the prognosis of RCC depends largely upon their morphological type and bearing in mind also, that precise diagnosis might mean the difference between therapeutic success and patient's death.

Materials and Methods

This was a 10-year retrospective descriptive study at the Department of Pathology, University College Hospital, Ibadan, Southwest Nigeria covering the period from 1st January 2007 to 31st December 2016. All the cases of histologically diagnosed renal cell carcinomas were obtained from the archival records of the surgical day books of the Department of Pathology for a period of 10 years spanning 1st January 2007 and 31st December 2016. Demographic data of all the 48 cases that met the inclusion criteria for this study were extracted from the archival records. All Hematoxylin and Eosin-stained slides of all cases of renal cell carcinoma in the surgical daybook of the Department within the study period were retrieved and reviewed by two Consultant Pathologists and this involved confirming the histological diagnosis to be renal cell carcinoma with appropriate subtyping of all the 48 cases of renal cell carcinoma seen based on the WHO classification of tumours of the kidney (2016).[12] The cases were subsequently graded using the Fuhrman grading system as well as the Chromophobe RCC tumour grading system for cases of Chromophobe RCC seen in this study.[13-16] In situations where the histologic slides of the cases could not be assessed or had faded, the paraffin embedded tissue blocks were retrieved, new sections made and stained. Cases whose slides or blocks could not be retrieved were excluded from the study.

The University College Hospital, Ibadan is an 1000-bed hospital and the premier tertiary health facility in the Southwestern region of Nigeria. It is a referral centre for other public and private hospitals in Ibadan and its environs. This study was conducted in accordance with the Helsinki declaration, maintaining confidentiality and dignity of patients. Patient names or other unique identifiers were not used in this study.

The data were analyzed using the Statistical Package for the Social Sciences Chicago, Illinois State (SPSS) software version 23 (IBM Corporation, SPSS Statistics Inc., USA, 2014). The Chi-square was used for categorical variables. The confidence level was set at 95% giving a level of statistical significance of 5% (p d" 0.05).

Ethical approval

Ethical clearance was obtained from the research committee of the Joint University of Ibadan/ University College Hospital, Ibadan Ethical Review Committee.

Results

There were a total of forty eight (48) cases of renal cell carcinomas (RCC) seen within this period that met the inclusion criteria for the study. The age range of the patients was between 3 to 76 years with an average age of 44.17 years. They were 21 males and 27 females with an approximate male to female ratio of 1:1.3. The most common morphological pattern seen in this study as shown in table 1, was clear cell renal cell carcinoma accounting for 30 cases

Table 1: Showing Morphological patterns of RCC

Morphological Patterns	Frequency	Percentage
Clear Cell	30	62.5%
Papillary	14	29.17%
Chromophobe	3	6.25%
Unclassified	1	2.08%
TOTAL	**48**	**100%**

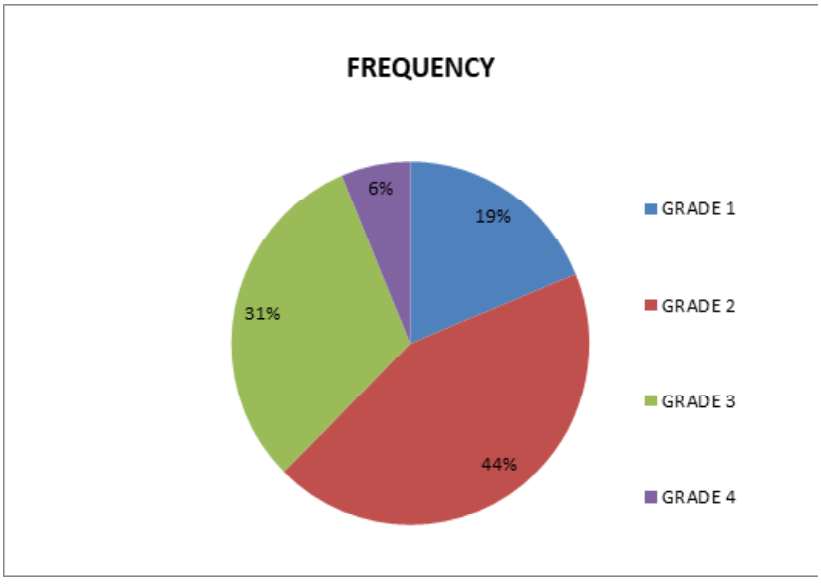
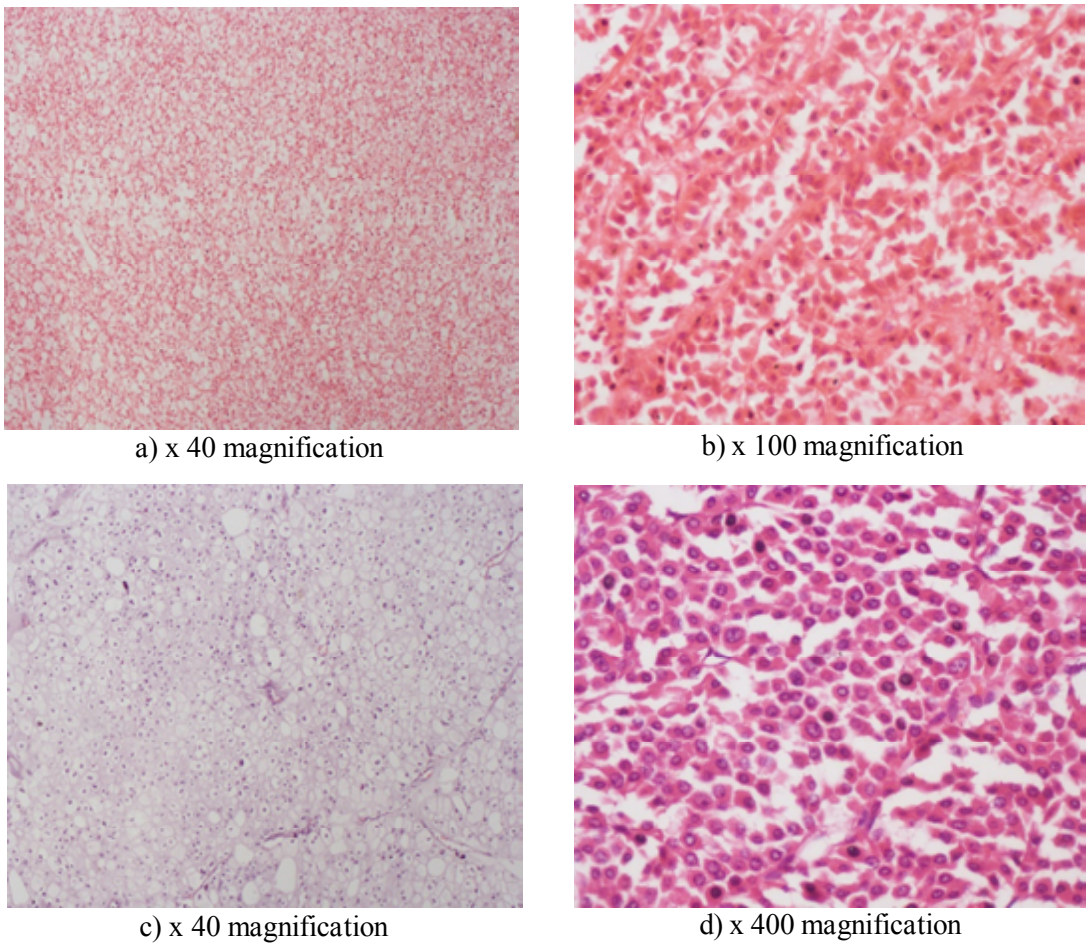


Figure 1: Showing frequency distribution of the Fuhrman grading of RCC

Table 2: Showing association between the morphological subtype and nuclear grading of RCC

Morphological sub type	Nuclear grading				Total	P value
	Grade 1	Grade 2	Grade 3	Grade 4		
Chromophobe	1	1	1	0	3	0.496
Clear Cell	6	14	8	2	30	
Papillary type 1	2	4	0	0	6	
Papillary type 2	0	1	6	1	8	
Unclassified	0	1	0	0	1	
Total	**9**	**21**	**15**	**3**	**48**	

$P < 0.05$



a) x 40 magnification

b) x 100 magnification

c) x 40 magnification

d) x 400 magnification

Figure 2: H&E staining of the histological variants of RCC: a) Clear cell RCC b) Papillary RCC c) Chromophobe RCC d) Unclassified RCC

(62.50%) followed by 14 cases of papillary RCC (29.17%) and then 3 cases of chromophobe renal cell carcinoma (6.25%). One case of unclassified variant of renal cell carcinoma was seen in this study (2.08%). The frequency distribution of the Fuhrman nuclear grading of RCC observed in this study showed that Grade 2 had the highest frequency (44%) followed by grade 3 (31%) and then grade 1 (19%). Grade 4 had the lowest frequency in this study (6%) as shown in figure 1. The association between the morphological patterns of RCC and the nuclear grading is as shown in table 2. Twenty out of the 30 cases of clear cell RCC which constitute the majority were low grade (i.e. grade 1 or 2) while the remaining 10 cases were high grade (grade 3 or 4). All the 6 cases of type 1 papillary RCC were low grade i.e. either grade 1 or grade 2 while most of the type 2 papillary RCC (7 out of 8 cases) were high grade.

The 3 cases of chromophobe RCC were grade 1, grade 2 and grade 3 respectively. The single unclassified variant was grade 2. The association between the morphological subtypes and the nuclear grading was however not statistically significant ($p>0.05$). Figure 2a to 2d showed the photomicrographs of the 4 histological variants of RCC seen in this study.

Discussion

This study investigated forty eight histologically diagnosed cases of renal cell carcinoma (RCC) at the University College Hospital, Ibadan, Southwest Nigeria over a 10-year period. The relatively few cases seen within this study period (average of 4.8 cases per year) is in keeping with the generally low yearly incidence of 4-5patients per year reported in Nigerian studies.[9,10,17] which also agrees with documentation in literature that RCC is a relatively uncommon malignancy in Africa.[9,17,18] The lower relative rates of RCC in Nigeria could be due to the fact that the reviews are limited to hospital-based statistics, as opposed to those from community-based cancer registries from the Western world.[19] This study is a follow up study to a previous similar study conducted by Odubanjo et al in Ibadan covering a period of 1960 to 2007.[22]

There were slightly more females than males in this study with a male to female ratio of 1:1.3 which is similar to the ratio of 1:1.2 and 1:1.7 reported in studies done by Akpayak *et al[20]* in Jos and Tijani *et al[9]* in Lagos, Nigeria respectively. This may be a reflection of the fact that the incidence of RCC has been found to be rising in women.[21] The mean age of the patients in this study was 44.17 ± 17.05 with an age range of 3-76years which is similar to some local studies done in different parts of Nigeria.[9,10,17,19,22] The observance of RCC at a younger age amongst Nigerians is in contrast to some international studies that reported higher mean ages of greater than 57years.[23,24]

The most common morphological pattern of RCC seen in this study was clear cell RCC making up 62.5%, followed by papillary RCC comprising 29.17% of the cases seen; this is similar to findings reported both globally[23,25-27] and locally,[9,10,17,19] where clear cell RCC was found to be the predominant RCC variant seen. The 14 cases of Papillary RCC in this study were further sub-classified based on morphological criteria[28] into type 1 in which the papillae were lined by a single layer of cells, mostly with low-grade nuclear features, and scant cytoplasm and type 2 in which there were pseudostratified nuclei of higher nuclear grade and abundant eosinophilic cytoplasm. Chromophobe RCC accounted for 6.45% of cases in this study and was the 3rd commonest morphological variant similar to the findings by Umar *et al* and Odubanjo *et al*.[19,22] The unclassified category which did not fit into any known morphological subtype of RCC was the least common variant in this study (2.08%) similar to the finding by Gudbjartsson *et al*.[29]

The Four-tiered WHO/ISUP grading system recommended by WHO was used to grade the morphological subtypes of RCC seen in this study into four nuclear grades[14,15]; grade 1-4, based on nucleolar prominence for grade 1-3 or pronounced nuclear pleomorphism, tumour giant cells and/or rhabdoid and/or sarcomatoid differentiation for grade 4.[14,15] Generally, the nuclear grade of the cases seen in this study were mostly low grade (grade 1 and 2) comprising 62.5% while cases with high grade nuclei (grade 3 and 4) were 37.5%. This finding is similar to the study by Odubanjo *et al[22]* in which 61.8% of cases reviewed had low grade nuclei. This suggests therefore that majority of the cases seen in our country are more likely to be low grade and therefore have relatively good prognosis which is consistent with global trend.[29,30] Most of the cases of clear cell RCC (66.7%) in this study were low grade in contrast to the study by Odubanjo *et al[22]* in which high grade nuclei were more common in clear cell RCC. All the 6 cases of type 1 papillary RCC were low grade while most of the type 2 papillary RCC (87.5%) were high grade consistent with findings in literature that type 2 papillary RCCs usually have higher grade nuclei.[25,28] The only unclassified variant was grade 2 similar to that reported by Gudbjartsson *et al*.[29] The association between the morphological subtypes and the nuclear grading was however not statistically significant ($p>0.05$) and this is consistent with findings in some studies.[22,29]

While the earlier study by Odubanjo et al found papillary RCC more common, this study found the clear cell variant as the predominant subtype. The clear cell variant is globally more common which shows that the pattern of RCC in Ibadan is aligning with the global patterns over the years. Similarly, the clear cell variants also have lower nuclear grades as against the previous study by Odubanjo et al. The implication of these findings therefore is the tendency to better prognostic RCC in Ibadan.

Genetics and cytogenetics studies would have told us whether these tumors are sporadic or familial. However, this study has not delved into the genetics of the RCC. Further studies would be necessary to unveiled the chromosomal aberrations that may be found in RCC such as deletions of Von Hippel Lindau gene on 3p.25.3 and somatic mutations or hypermethylation-induced activation of the same gene in clear renal cell carcinoma.

Conclusion

Renal cell carcinomas are relatively rare in our environment and tend to occur at an earlier age with most cases being low grade. Clear cell variant is probably the predominant morphological subtype of renal cell carcinoma in Ibadan differing from a previous local study and in keeping with many studies locally and globally. More community-based studies are needed to determine the incidence of renal cell carcinomas. It is also necessary to carry out further genetic studies to determine whether these cancers are mainly familial or sporadic.

Limitation

The study was done in a single tertiary hospital in Southwest Nigeria and may not be fully representative of the situation in our entire Country.

Conflicts of Interest

There are no conflicts of interest.

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