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Histologic subtypes of renal cell carcinoma diagnosed in the University of Witwatersrand Teaching Hospitals

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Histologic Subtypes of Renal Cell Carcinoma Diagnosed in the University of Witwatersrand Teaching Hospitals.

A research report submitted to the Faculty of Health Sciences of University of the Witwatersrand in partial fulfilment for the degree of Master of Medicine in Urology by:

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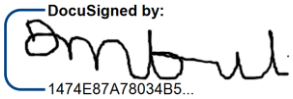
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Dr M Nel

DECLARATION

I, Dr. Solomon Terumbul Orsar declare that this research has been solely carried out by me and it is submitted for the degree of Master of Medicine in Urology in the University of Witwatersrand, Johannesburg in the Republic of South Africa.

This research has not been submitted for examination in whole or in part to this university or any other university before. Except where stated otherwise by reference or acknowledgement, the work presented is entirely my own.



Solomon Terumbul Orsar

Date: 06/11/2021

DEDICATION

I dedicate this research to The Almighty God, my creator, guide, protector and to the memory of my father: Papa Joseph Gogo Usar-Ikpa who passed onto glory while this dissertation was being written.
I also dedicate it to my beautiful wife Patience Sih Orsar and our lovely children who have stood by, and supported me through every moment.

I would not have come this far without your unflinching love and support. I am, and will be eternally grateful.

I love you all.

ABSTRACT:

Introduction:

Renal cell carcinoma and its histologic subtypes is the most common renal parenchymal tumour and occur globally with regional variations and increasing incidence. The incidence rate is higher in North America and Europe but lower in Asian and African countries.

Objectives:

To determine the incidence of renal cell carcinoma as diagnosed in the University of Witwatersrand Teaching hospitals and the proportion of patients less than 40 year as well as stratify its subtypes according to patient demographics;

To compare its occurrencein the local populations with international racial groups.

Methods:

Histopathologic data was retrieved from the National Health Laboratory Service and analysed after obtaining all the necessary approvals.

Results:

Analysis of the data showed racial disparity of the histologic subtypes and gender distribution as compared to Western populations as well as a significant proportion of

Patients less than 40 years.

Conclusions:

There is racial disparity in incidence of histopathologic subtypes of renal cell carcinoma and its occurrence is statistically significant in patients less than 40 year.

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LIST OF ABBREVIATIONS:

AJCC: American Joint Committee on Cancer

ARCD: Acquired Renal Cystic Disease

BPDE: Benzo-α-Pyrene- Diol Epoxide

CEOs: Chief Executive Officers

DNA: Deoxyribonucleic Acid

ESRD: End Stage Renal Disease

HREC: Human Research Ethics Committee

NSAIDs: Non-Steroidal Anti-inflammatory Drugs

NNK: Nicotine-derived Nitrosamine Ketone

NHLS: National Health Laboratory Service

RCC: Renal Cell Carcinoma

SEER: Surveillance, Epidemiology and End Result

TCE: Trichloro-Ethylene

TNM: Tumour Node, Metastasis

USA: United States of America

VHL: Von Hippel-Lindau

Histologic subtypes of renal cell carcinoma in the University of Witwatersrand Teaching Hospitals.

CHAPTER 1

1 LITERATURE REVIEW

1.1 INTRODUCTION

Renal cell carcinoma (RCC) makes up about 3% of all adult cancers, and has the highest incidence of all renal cell cancers arising from the renal parenchyma with an occurrence of 90 -95%. The other renal cancers include: transitional cell carcinoma, renal sarcoma, Wilm's tumour, lymphomas and secondary malignancies (1–4). RCC is a heterogeneous group of tumours, with a number of histological subtypes, molecular features and different treatment outcomes (2, 3, 5, 6)

RCC affects mainly adults between 50-70 years of age, but may occur earlier in the genetically predisposed individuals, especially in the under 40 years of age (2, 4, 7, 8) In the paediatric age group, RCC, mesoblastic nephroma and multilocular cystic nephroma collectively represents less than 10% of all renal tumours. (9).

There are three common and several less common histologic subtypes of RCC:

1.1.2 Common histologic subtypes of RCC

1. Clear cell RCC: Accounts for 80-90% of RCC,
2. Papillary RCC: 10-15%,
3. Chromophobe RCC: 4-5%.

(See Table 3.1)

1.1.3 Less common histologic subtypes of RCC

4. Multi-loculated cystic RCC,
5. Collecting duct carcinoma (Bellini duct carcinoma),
6. Medullary renal cell carcinoma,

7. Mucinous tubular and spindle cell RCC,
8. RCC associated with short arm chromosome Translocation Xp11,
9. Post neuroblastoma RCC,
10. Unclassified RC .

(1,4,5)

1.2 EPIDEMIOLOGY

In 2012, RCC had a world-wide incidence of 337 860 cases (213 924 men; 123 936 women), depicting a male to female ratio of 2:1 and a total death of 143 406 (90 802 men; 52 604 women). A positive correlation of 0.731 was found between Standardized Incidence Rates (SIRs) of kidney cancer and human development index (HDI), that is a long and healthy life, being knowledgeable and having a decent standard of living (10). This incidence, however, differs from region to region with more than 15/100 000 in several Northern and Eastern European countries such as the Czech Republic, Lithuania, Latvia, Estonia, Iceland and also among African Americans with an approximate male to female numbers of 22/100 000 and 9.9/100 000 respectively, while it is 1/100 000 in African countries with intermediate rates recorded among USA, Canadian, Australian, and New Zealand whites (4,11).

In South Africa, the 2017 Cancer Association of South Africa Fact Sheet on Kidney Cancer showed a RCC incidence of (766/56 520 000) population, which is 1/100 000 with a male to female ratio of 2:1 **(12).** In the USA, a higher incidence of the papillary histologic subtype of RCC was seen in the African American population while the clear cell subtype predominated in the white population (13).

Actuarial sciences estimated the general life time risk for developing RCC in the USA as 1.6%, based on the 2012 data of the National Cancer Institute: Surveillance, Epidemiology and End Result Program (SEER data). These data show an incidence increase of 3-4% per year across all ages and racial groups with a doubling of incidence in men up to the age of 70 to 74 years. This observation may be partly due to increased

abdominal imaging as an investigative tool, which has inadvertently increased incidental RCC detection by 30-40% (6).

1.3 RISK FACTORS

1.3.1 Demographic risks factors

The incidence of RCC is noted to be substantially lower in Asians, both in Asian countries and in the USA, higher in African Americans and Hispanics men who presents at a younger age with poorer prognosis than in their white population, but lower in Africans in African countries. These racial disparities in incidence are thought to be partly due to differences in genetic predisposition, accessibility of health care, incidence of hypertension, socio-economic and environmental factors (4, 14–17).

1.3.2 Aetiologic factors in RCC

1.3.2.1 Genetic and germline mutations

Hereditary types of RCC are usually autosomal dominant in inheritance, show bilaterality or multi-focality, occur earlier in life in the third to fifth decade and are associated with extra-renal manifestations. They include:

i. Von Hippel–Lindau (VHL) syndrome: Due to a mutation in the VHL tumour suppressor gene on chromosome 3p25, this normally functions as a suppressor of hypoxia inducible factors for ubiquitin-mediated degradation. This mutation results in unchecked production of these inducible factors that up regulate vascular endothelial and platelet derived growth factors and others that promote angiogenesis and growth of typically hypervascular tumours, pheochromocytomas, paragangliomas, cystadenomas of the epididymis or broad ligament, retinal angiomas, endolymphatic sac tumours, and hemangioblastomas of the cerebellum, brain stem and spinal cord.

ii. Hereditary papillary renal cell carcinoma (HPRCC): Type I papillary: due to mutations in the C-met proto-oncogene on chromosome 7.

iii. Hereditary leiomyomatosis and RCC: Type II papillary is associated with multiple fibroids and cutaneous leiomyomata. The mutation is in the fumarate

hydratase gene on chromosome 1, and the tumours are aggressive and metastatic in 50% of cases.

iv. Birt–Hogg–Dubé syndromes: This mutation affects the folliculin gene on chromosome 17. Associations include: cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothoraces, and RCC. May present with a combination of various histologic subtypes of RCC occur like chromophobe RCC, oncocytoma, and, rarely clear cell carcinoma.

v. Xp11.2 translocation/TFE3 gene fusion RCC: This is due to fusion of the gene that causes the translocation of TFE3 on chromosome Xp11.2 to another chromosome. It is a highly invasive and metastatic renal disease. (2, 4, 7, 8,16)

1.3.2.2 Smoking

Smoking increases the risk of developing RCC by up to 2.3 fold compared to individuals who never smoked. This risk depends on the intensity and duration of smoking and is associated with presentation of advanced carcinoma. However, the RCC risk decreases after ten or more years of smoking cessation. Thus, the higher the pack year history of smoking, the higher the risk of presenting with advanced RCC. Carcinogens in cigarette smoke induce biologic mechanisms, damage the renal tubules, and also alter haemodynamics as well as the body's response to oxygen radicals. Two of the most important carcinogens in cigarette smoke include:

i. 4-methylnitrosamino-1-(-pyridyl)-1butanone (NNK), which is an N-nitrosamine which damages DNA in the peripheral blood lymphocytes resulting in increased risk of RCC.

ii. Benzo-a-pyrene-diol epoxide (BPDE) which causes chromosomal abnormality at the 3P locus with consequent increased susceptibility to developing RCC (7, 16, 18)

1.3.2.3 Obesity

The association of excess body weight and RCC is stronger in women than in men. This is thought to be attributable to the increased production of sex steroids and oestrogen (7,18).

1.3.2.4 Hypertension

Hypertension increases the RCC risk by two fold with an odds ratio of 1.9 for USA whites and 2.8 for African Americans. This risk doubles after 25 years of diagnosis, especially if hypertension is poorly controlled (7,18).

1.3.2.5 Acquired Renal Cystic Disease (ARCD)

Acquired renal cystic disease (ARCD) is seen in 35-50% of patients with end stage renal disease (ESRD) on chronic haemodialysis of which 6% eventually develop RCC. Overall, there is an approximate 30% increased risk of ESRD patients to develop RCC compared with the general population. The RCC risk is proportional to the duration of dialysis and these patients present at a younger age than the general population. (4,19).

1.3.2.6 Occupational exposure

Occupational exposure to toxic compounds, such as pesticides, benzene, herbicides, trichloroethylene (TCE), cadmium, asbestos, and petroleum by-products, has an approximate 2

fold higher risk of RCC than the general population. A cohort study in Australia in 4396 prebake aluminium smelters showed a two-fold increase in risk of kidney cancer.(4,7,18, 20).

The relationship between mutations in the Von Hippel-Lindau (VHL) tumour suppressor gene and exposure to trichloroethylene (TCE), a petroleum by-product used as a metal degreaser, was evaluated in 44 patients with RCC known to have been exposed to the toxin. A VHL mutation was found in 33 of the 44 RCC patients, though two subsequent studies were not conclusive on TCE causation of RCC. (4, 7, 18)

1.3.2.7 Analgesic use

Routine and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) is a known risk factor for RCC. This was confirmed by the finding of a large prospective study that included 77 525 women followed over a period of 16 years and 49 043 men followed over 20 years. This risk is however not associated with the controlled use of aspirin or acetaminophen (21).

1.3.2.8 Radiation

Ionizing radiation treatment of immunological (e.g. ankylosing spondylitis) and some malignant conditions (e.g. cervical cancers and neuroblastoma in children) predisposes treated individuals to development of RCC (22).

1.3.2.9 Nutrition and dietary factors

Diet may play a role in the development of RCC. Westernization of diet coincides with increasing incidence of RCC in Asia, suggesting a link between increased intake of fats and proteins and RCC (23).

CHAPTER 2

2.1 Research questions

1. What are the incidences of histologic subtypes, pathological stages and grades of RCC diagnosed in the University of the Witwatersrand Teaching Hospitals?
2. Do the frequencies of occurrence of these RCC subtypes differ from other African and Western populations?

2.2 Aims and objectives

2.2.1 Aims

The aim of this study was to determine the frequency and occurrence of the histologic subtypes, pathologic stages and grades of RCC diagnosed in the University of the Witwatersrand teaching hospitals.

2.2.2 Objectives

1. To stratify RCC histologic subtypes diagnosed in the University of the Witwatersrand teaching hospitals by age, gender, race, pathological stage, grade and metastatic status.
2. To compare the frequency of occurrences of RCC histologic subtypes found with other African and Western populations.
3. To determine the number of patients less than 40 years diagnosed with RCC and statistically compute the tallied numbers for significance.

2.3 Methods

1. Accessing and obtaining confirmed RCC histologic data from the National Health Laboratory Services for subtypes and grades of RCC.
2. RCC staging: was according to the American Joint Committee on Cancer and Tumour Size, Lymph Nodes affected, Metastasis (AJC and TNM) staging system graded: 1-4. This indicates the size of the cancer in an organ in the body, whether it is confined to, has extended into surrounding tissues/organs or has spread beyond

the confines of the primary organ of origin. The higher the grading number, the more the extent of primary organ and or adnexal tissue involvement.

3. Assessment for metastasis was based on the primary diseased organ and any additional tissues submitted for histopathological evaluation.
4. Evidence of malignancy in any lymph node submitted for histological assessment was recorded as metastasis.
5. Patient hospital files were reviewed for demographic data such as race, age and gender only.
6. Determination of frequency and significance of RCC occurrence relating to race, age and gender.
7. Fuhrman grading: Based on the degree of abnormal cell differentiation, which shows nucleic structure appearing progressively more bizarre compared to the normal nucleus, as the grading number increases (graded from 1-4 as per Table 2.1).

Table 2.1 Fuhrman grading 1-4

Grade	1	2	3	4
Nuclear size	10µm	15µm	20µm	>20µm
Nuclear shape	Round	Round	Irregular	Bizarre
Nucleoli	Inconspicuous	Seen @ X400	Seen @X100	Multi-lobed

8. The staging system currently in use is the World Health Organisation/International Society of Urological Pathology (WHO/ISUP) system which is based on the evaluation of the nucleoli:

Grade 1 tumours have nucleoli that are inconspicuous and basophilic at ×400 magnification

Grade 2 tumours have nucleoli that are clearly visible at ×400 magnification and are eosinophilic

Grade 3 tumours have clearly visible nucleoli at ×100 magnification

Grade 4 tumours have extreme pleomorphism or rhabdoid and/or sarcomatoid morphology.

2.4 Study design

This study was a retrospective review of records and data of RCC histologic subtypes diagnosed in the University of the Witwatersrand teaching hospitals over a 10-year period from 1st January 2008 to 31st August 2018. It was carried out at the Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Helen Joseph Academic Hospital.

The study reviewed histologic data of pathologically confirmed RCC surgical patients diagnosed in the Urology Units of the three teaching hospitals of the University of the Witwatersrand. These Urology Units manage an average of 45 600 patients per annum and have seven full-time consultants. These three Urology Units offer patients a wide range of tertiary urology care including surgical, medical and oncologic services. These hospitals cover and receive patients from Germiston, South Rand, Edenvale, Leratong, Hillbrow, Yeoville, Alexandra and Johannesburg hospital areas, including parts of Pretoria and even the Free State Province.

2.5 Study population

The study population was all patients pathologically diagnosed with RCC in the University of the Witwatersrand teaching hospitals from 1st January 2008 to 31st August 2018.

2.6 Study procedure

The histologic records of all patients diagnosed with RCC at the three mentioned teaching hospitals, within the 10 year study period, were retrieved after obtaining approval from the hospital CEOs, the data gatekeeper, Prof MJ Hale, of the National Health Laboratory Services (NHLS) and Ethical clearance from the Human Research Ethics Committee (medical) of the University of the Witwatersrand with number: M180821 dated 31 August 2018. Information on age, gender and the histological subtypes, grades and metastatic status was extracted and statistically analysed.

2.7 Inclusion criteria

All complete records/data on RCC histopathological samples collected by the Histopathology Departments of the University of the Witwatersrand teaching hospitals and confirmed as RCC by the NHLS between the 1st of January 2008 and the 31st of August 2018 were included in the study.

2.8 Exclusion criteria

Any histologic records/data not indicating the RCC subtype.

2.9 Statistical analysis

Data obtained from the Histopathology Department was entered into an Excel spreadsheet in Windows. The Excel spreadsheet was imported into statistical product and service solution (SPSS) version 25, for statistical analysis. The categorical socio-demographic characteristics of the patients were described by using frequency and percentages. Continuous variables such as age were described using the mean (standard deviation) or the median (interquartile range) depending on the distribution of the variable. The 95% confidence interval and the p-value of analysed RCC relationships were calculated.

Comparison of the mean age of the patients by ethnicity and histological RCC subtype was conducted by using the analysis of variance. The association between the categorical demographic variables and the histologic subtype was investigated by using the Pearson's Chi Square test.

2.10 Ethics

Permission was obtained from the CEOs of the Charlotte Maxeke Johannesburg Academic Hospital, the Chris Hani Baragwanath Academic Hospital and the Hellen Joseph Academic Hospital as well as the data gatekeeper, Prof MJ Hale of the NHLS to access patient records and obtain histologic data for this study (Appendices: A B, C and D). Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) (medical) with study number: M180821 (Appendix: E) before commencement of the study.

Strict confidentiality of the data was ensured and all data was collected anonymously by using only a research study number without any patient identifiers. A password protected computer was used to store the data.

CHAPTER 3

3.0 RESULTS

3.1 Age distribution in the diagnosed RCC patients

A total of 206 histopathological confirmed RCCs of various histological subtypes were diagnosed in individuals with an age range of between 19 to 79 years and a mean age of 61.4 years (Figure 3.1).

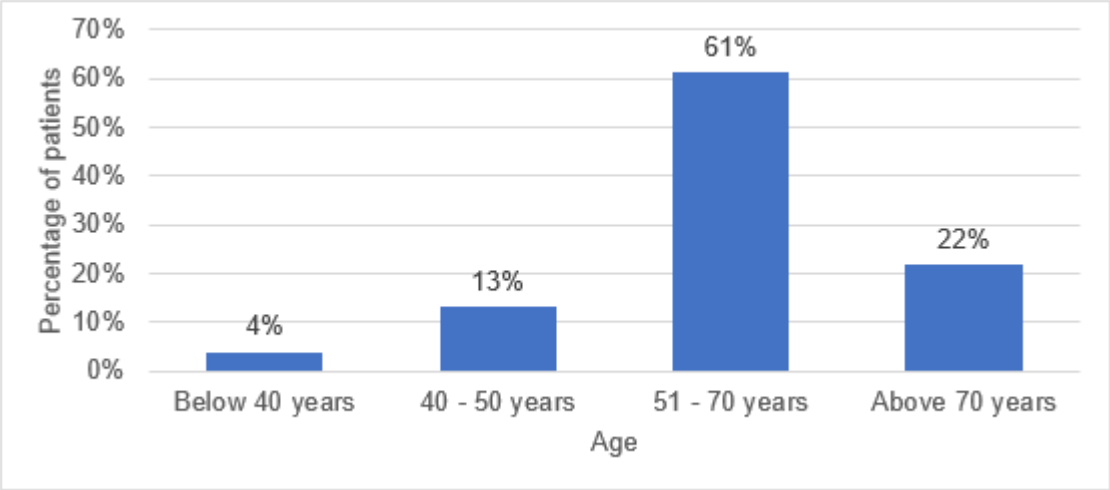


Figure 3.1 Patient age distribution.

3.2: RCC distribution by gender

This study showed the total males diagnosed with RCC was significantly higher than the female numbers recorded, which equates to a male to female ratio of 3.8:1 (Table 3.1).

Table 3.1 RCC distribution by gender

	Numbers	Percent
Male	163	79%
Female	43	21%
Total	206	100%

3.3 Number of Patient by histopathologic RCC subtypes

The histopathological subtype distribution found among the 206 patient records was as shown in Table 3.2.

Table 3.2 Numbers of patients by RCC subtypes

Histology	Numbers	Percent
Clear Cell	171	83.0%
Papillary type	28	13.6%
Chromophobe	1	0.5%
Multi-loculated cystic	6	2.9%
Total	206	100.0%

3.4 Histopathologic subtype distribution by race

The results show that clear cell RCC was the most prevalent histologic subtype in all racial groups compared to other histologic subtypes for each race. Although the frequency of occurrence of clear cell RCC cases in black Africans were higher compared to whites and Indians/Asians, there was no statistically significant difference amongst the different races (p-value = 0.99) (Table 3.3).

Table 3.3 RCC subtype distribution by race

		Race				
Variable	Tumour type	Black	White	Indian	Total	p-value
Histopathology	Clear cell	138 (82.0 %)	17 (85%)	16 (88.9%)	171 (83.0%)	0.99
	Papillary type	24 (14.3%)	2 (10%)	2 (11.1%)	28 (13.6%)	
	Chromopobe					
	Multi-loculated cystic	1 (0.6%)	0 (0%)	0 (0%)	1 (0.5%)	
		5 (3%)	1 (5%)	0 (0%)	6 (2.9%)	

The papillary type 1 histologic subtype was identified across all racial groups, while the papillary 2 histologic subtype was only diagnosed in black Africans (Table 3.4).

Table 3.4 RCC subtype distribution by race with the papillary subtypes indicated

Variable	Tumour type	Race			Total	p-value
		Black	White	Indian		
Histopathology	Clear Cell	138 (82.0 %)	17 (85%)	16 (88.9%)	171 (83 %)	0.99
	Papillary type1	15 (8.9%)	2 (10%)	2 (11.1%)	19 (9.2%)	
	Paillary type2	9 (5.4%)	0 (0%)	0 (0%)	9 (4.4%)	
	Chromophobe	1 (0.6%)	0 (0%)	0 (0%)	1 (0.5%)	
	Multi-loculated cystic	5 (3%)	1 (5%)	0 (0%)	6 (2.9%)	

3.5 Histopathologic subtype distribution by age

The number of patients below 40 years diagnosed with RCC is statistically significant compared to patients above this age (p-value = 0.001) (Table 3.5).

Table 3.5 Histopathologic subtype distribution by age

Histopathology by age and RCC subtype							
							Total
			Below 40 years	40 - 50 years	51 - 70 years	Above 70 years	
Histopathology	Clear Cell	Count and (%)	5(2.4 %)	19(11.2%)	108(63.5%)	39(22%)	170(100%)
	Papillary type 1	Count and (%)	2(10.5%)	4(21.1%)	10(52.6%)	3(15.8%)	19(100%)
	Papillary type	Count and	0(0.0%)	3(33.3%)	6(66.7%)	0 (0.0%)	9(100%)

	2	(%)					
	Chromophobe	Count and (%)	0(0.0%)	0(0.0%)	0(0.0%)	1(100%)	1(100%)
	Multi-loculated cystic	Count and (%)	1(16.7%)	1(16.7%)	2(33.3%)	2(33.3%)	6(100%)
Total		Count and (%)	8(3.9%)	27(13.1%)	126(61.2%)	45(21.8%)	206(100%)

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	43.737	18	0.001
n of Valid Cases	206		

3.6 RCC staging

In the study population, 73 patients (PT1) 35.4% were low risk, 104 (PT2) 50.5% were intermediate and 29 (PT3-4) 14% were high risk. Although it is not possible to be certain of the exact staging of these tumours, 85.9% were intermediate or low risk and 14% were high risk as per the pathological T staging only (Table 3.6).

Table 3.6 Histopathologic stages of diagnosed RCC (AJCC and TNM system)

Pathological stage	No.	Percentage
T1a	**32**	**16%**
T1b	**41**	**20%**
T2a	**65**	**32%**
T2b	**39**	**19%**
T3a	**22**	**11%**
T3b	**5**	**2%**
T4	**2**	**1%**
Total	**206**	**100%**

3.7 Fuhrman's grading and staging of RCC

A total of 150 (73%) cases were low grade tumours (stages 1 and 2) and 56 (27%) cases were high grade tumours (stages 3 and 4) according to the Fuhrman grading and staging systems (Table 3.7).

Table 3.7 Fuhrman's RCC grading in diagnosed patients

Fuhrman's Grade	Patient numbers	Percentage
1	49	24%
2	101	49%
3	53	26%
4	3	1%
Total	206	100%

3.8 Metastasis

Node status could only be assessed in 47/206 of which 13 only were positive. Node status could not be assessed in most (159) patients (Table 3.8). Metastasis were found in 8 patients, in whom spread involved non-regional lymph nodes or distant metastasis, while in the majority of cases (197) metastasis was not assessable (Table 3.9).

Table 3.8 numbers of patients with metastatic nodal involvement.

Nodes	Numbers	Percent
N0	34	17%
N1	13	6%
Nx	159	77%
Total	206	100%

Table 3.9 numbers of patients with metastatic disease

Metastasis	Numbers	Percent
M0	1	0.5%
M1	8	3.9%
Mx	197	95.6%
Total	206	100.0%

3.9 Trend of the incidence of RCC from 1st Jan 2008-31ST August 2018

The RCC diagnosis steadily increased from 2010 to 2015, plateaued in 2016 and then showed a downward trend from 2017 to August 2018 when data collection was stopped at the end of the study period (31st of August 2018) (Table 3.10 and Figure 3.3).

Table 3.10 Number of RCC patients diagnosed per year over the 10 year study period

Year	Number	Percent
2008	10	4.9
2009	9	4.4
2010	7	3.4
2011	15	7.3
2012	0	0
2013	29	14
2014	26	12.6
2015	33	16.0
2016	31	15.0
2017	29	14.1
2018	17	8.3
Total	206	100.0

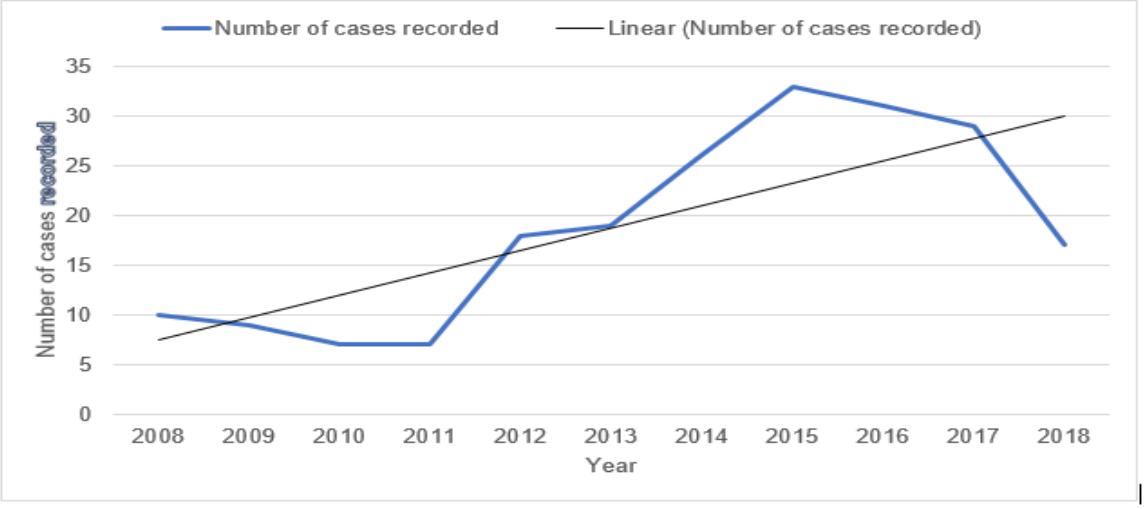


Figure 3.2 Trend of RCC occurrence over the 10 year study period

CHAPTER 4

4.1 Discussion

Renal cell carcinoma is the predominant malignancy of the kidney and has several histologic subtypes that show varying geographic, regional, demographic and ethnic/racial presentations. Classic clinical presentation includes abdominal/flank mass with or without pain and haematuria with or without constitutional symptoms. Diagnosis is based on clinical, imaging and histopathologic findings upon which appropriate therapeutic measures are instituted.

Various risk factors although not specifically studied here include: demographics, obesity, hypertension, ARCD, occupational exposure to toxic compounds, tobacco smoking, analgesic usage and radiation. Genetic predispositions are associated with the development of RCC subtypes such as the Von Hippel-Llindau syndrome, the Birt-Hogg-Dube syndrome, the papillary subtypes I and II and the Xp11.2 translocation/TFE3 gene fusion. These genetic factors predispose an individual to RCC which is characterized by early age onset, multi-focality and bilaterality of RCC tumours (3, 4).

4.1.1 Age distribution of RCC (Figure 3.1)

The study results showed that eight (4%) patients were younger than 40 years, 27 (13%) were 40-50 years, 126 (61%) of patients were 51-70years and 45 (22%) were older than 70 years. The higher occurrence of RCC at ages above 50 is similar to those recorded internationally in North American and Western Europe (15). However, the mean age of the 206 patients in our study was 61.4 years, this mean is slightly lower than the 64 years quoted for American Whites, but similar to African and Hispanic Americans in a California Cancer Registry report by Stafford HS et al., (15, 24). This difference may reflect differences in earlier exposure to risk factors, genetic predisposition or higher incidence of comorbidities such as hypertension; obesity etc. Further multicentre investigations may better explain the reason for this difference.

4.1.2 Gender distribution of RCC subtypes (Table 3.1)

This study showed the total males diagnosed with RCC as 163 (79%), while the female numbers were 43 (21%). This equates to a male to female ratio of 3.8:1. A higher male proportion was similarly reported by Agnihotri et al., in an Indian population study (25). This is significantly different from the conventional ratio reported in Europe and North America as 2:1 (2, 18, 26).

Since this was a retrospective study based on retrieved data, it was not possible to elucidate the specific factors that might have been responsible for such a high male ratio. Possible explanations include increased male exposure to environmental risk factors discussed above, especially occupational exposure to toxic substances and the fact that more males smoke and are exposed to tobacco smoking or higher male hospital attendance. This area requires further investigation for clarification.

4.1.3 Number of the RCC subtypes (Table 3.2)

The histopathological subtype distribution found among the 206 patients recorded was as follows: Clear cell: 171 (83%), Papillary subtype: 28 (13.6%), Multi-loculated cystic: 6 (2.9%) and Chromophobe: 1 (0.5%). This high preponderance of the clear cell histological subtype followed by the papillary subtypes concurs with the findings of Ezenwa and Tan and other researchers (14). However, unlike the 5% occurrence attributable to the chromophobe RCC subtype in North America and Western Europe, this study found only 1% in the study sample. The rarity of the other subtype such as Xp11.2 translocation/TFE3 gene fusion RCC in this study, which has been reported to make up 20% of RCC in the paediatric age group and adolescent; may reflect the absence of appropriate immuno-histochemical staining facility within the University of Witwatersrand laboratories in the study period (5).

4.1.4: Subtype distribution by race (Tables 3.3, and 3.4)

The results show that clear cell RCC was the most prevalent histologic subtype in all racial groups compared to other histologic subtypes for each race at 81.5% in black Africans, 85% in whites and 88.9% in Indians/Asians. The papillary type I histologic

subtype was also identified across all racial groups, while papillary 2 subtype was only diagnosed in black Africans. The preponderance of papillary subtype II in the South African population was previously reported by Du Plessis *et al.* (27).

Although the numbers of clear cell RCC cases in black Africans were higher (168 (82%)) compared to whites (20 (10%)) and Indians/Asians (18 (9%)), there was no statistically significant difference in the frequency of occurrence of the clear cell subtype amongst the different races (p-value = 0.99).

This may be explained by the fact that statistical analysis for frequency of occurrence of RCC subtypes were done independently for each race. Because the total numbers of patients in each race were significantly different, the apparent higher clear cell RCC numbers recorded in the black South Africans only reflect their higher representation in the study sample, and not necessarily a higher frequency of subtype occurrence and is thus not statistically significant.

This study also indicates that Asians/Indians have the lowest occurrence of RCC amongst the South African population studied, which concurs with published international research studies also noting lower incidence in Asians both living in America and their countries/ regions (4, 28, 29, 30).

4.1.5: Histopathologic subtype distribution by age (Table 3.5):

The results shows that eight patients (4%) were younger than 40 years, 27 (13%) patients between 40 and 50 years of age and 175 (85%) above 50 years. The number of patients below 40 years diagnosed with RCC is statistically significant (p-value = 0.001). This finding is of importance, because diagnosis of RCC in this age group is usually related to genetic/germline mutations. The 4% incidence in the under 40 years seen in this study reflects the generally accepted frequency of association of familial and genetic causation of RCC (2, 8).

Internationally, researchers proffer that diagnosis of RCC in this age group and younger, even without other syndromic/clinical manifestation/s (e.g. cerebral haemagioblastoma, retinal angiomas, pancreatic cysts; uterine leiomyosarcoma, lung cysts etc.) or a positive family history, should prompt genetic counselling and testing. (4, 8).

4.2: RCC staging (Table 3.6):

In the study population, 73 patients (PT1) 35.4% were low risk, 104 (PT2) 50.5% were intermediate and 29 (PT3-4) 14% were high risk. Though it is not possible to be certain of the exact staging of these tumours, 85.9% were intermediate or lower risk and 14% high risk going by the pathological T staging only. The increased diagnosis at earlier stages may be a reflection of increased abdominal imaging for unrelated abdominal pathologies with incidental pick up of RCC. This finding and possible reason is similarly reported in international studies (6, 31, 32).

4.3: Fuhrman grading: (Table 3. 7, Fig. 3.2)

A total of 150 (73%) cases were low grade tumours and 56 (27%), high grade tumours by the Fuhrman grading system.

4.4: Metastasis: Tables 3.8, 3.9):

Node status could only be assessed in 47/206 (23%) of cases, of which 13 (6%) were positive. It could not be assessed in 159 (77%) patients. This may be due to that fact that lymph nodes were not submitted for histological evaluation.

Metastasis were found in 8 (3.9%) patients, in whom spread had involved non-regional lymph nodes or distant metastasis (cancer involvement of tissues/organs around, or different sites from the kidney), and not assessable in 198 (96%) of cases. This study could not evaluate for metastatic disease in 198 of the cases because the histopathologic report did not contain information on metastasis, neither were their clinical notes nor imaging reviewed for this purpose since this was not an objective of the study. This is recognized as a short coming of this study.

4.5: Trends: (Table 3.10; Fig 3.3):

The RCC diagnosis steadily increased from 2010,flattened out in 2012 then increased again up to 2016 then showed a downward trend towards the end of 2016 to 31st of August 2018 when data collection was stopped at the end of the study period.

The noted increase in diagnoses may possibly be explained by the increased use of general abdominal imaging for urological/non-urological purposes, which resulted in more incidental diagnosis of RCC. Closely related to this possibility is the higher diagnosis of low grade tumours: 150 (73%) and low risk': 138 (67%) RCC tumours (31-33). These findings agree with a previous South African study by Du Plessis, Van Deventer, Fernandez (27); and contrasts with the perception that RCC patients mostly present at advanced stages of the disease in the developing world with less favourable prognosis (25). The favourable stage migration may be due to community education and awareness of risk factors as well as better access to health facilities and imaging studies.

Noteworthy is the decrease in diagnosis of RCC in 2017 and 2018 which may be due to an increased South African population awareness of RCC related risk factors known to increase incidence of RCC with their adoption of healthier lifestyle choices or partly due to absence of data in 2012 and only the first eight months of data collected in 2018. However, the downward trend started in 2017 and continued in 2018. International studies have also noted a decreasing trend in RCC incidence and is thought to be due to awareness and reduction in exposure to risk factors, as well as plateauing of imaging utilisation (31).

4.6: International variations

This study showed a higher male: female ratio in RCC prevalence of 3.8:1 than conventionally reported in international studies (25, 34). This maybe a reflection of a local variation of gender presentation in the South African population, differences in the utilisation of public and private hospitals, some socio-economic factors or

disproportionately higher exposure of the male gender to environmental risk factors. This may be further clarified by future multi-centre investigations.

4.7 Conclusions

To the best of our knowledge, this is the first South African study that has specifically investigated the proportion of patients under 40 years diagnosed with renal cell carcinoma and has determined that the numbers are statistically significant, which has very important genetic/germline mutation implications.

The traditional approach in the University of the Witwatersrand teaching hospitals is to offer specific and appropriate RCC directed treatment without the genetic counselling component. This approach might have resulted in missed opportunities of offering genetic counselling/testing to patients and family members, as well as missed appropriate surveillance/follow-up for the genetically predisposed.

With this finding, urologist will better serve the population if genetic counselling is incorporated into appropriate routine uro-oncology practice to enable early diagnosis, better chance of curative treatments, preservation of renal function and avoidance of long term complications.

4.8 Limitations of this study

Our study was a retrospective epidemiological study that evaluated RCC histological report in the NHLS data base and demographic data in the patient clinical files, thus we were only able to ascertain the pathological tumour stages based on limited information.

Limitations included:

1. The Fuhrman grading system used by NHLS during the study period is known to have issues with reproducibility, validity and interpretation.

2. The apparent rarity of occurrence of the Xp11.2 RCC subtype in this study is likely due to the unavailability of the appropriate immuno-histochemical staining during the

majority of the study period. Thus, it is not recorded separately but place with clear cell RCC; with which, it has similar histological appearance.

3. The staging/metastasis information available to this investigator limits the accuracy and comprehensiveness of staging these patients. Since this was neither a goal nor objective of this study, radiological and clinical note reviews for this purpose were not done, thus, information obtained was limited to the analysed specimens submitted to histopathology laboratory for evaluation.

4.9 Recommendations

We recommend that further multicentre studies be done to confirm our finding of significant occurrence of RCC in patients less than 40 years which should then lead to institutionalization of genetic/germline mutation counselling and testing in these age group in the University of the Witwatersrand Teaching hospitals and other uro-oncology centres in South Africa.

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