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Management of Advanced Renal Cell Cancer in South-South Nigeria

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Abstract | **Original Research Article**

Renal cell carcinoma (RCC) constitutes 2-3% of cancers worldwide and the majority present in advanced stages in our environment. The aim was to determine the prevalence, demographics, clinical presentation, histological type and management of RCC in our centre. ***Patients and Methods:*** Retrospective data from records of patients treated with RCC between January 2012 and December 2021 were analysed. Patients' age, clinical presentation, investigations, tumour stage, histopathology, treatment, and outcome were documented. ***Results:*** Nineteen patients were seen over a ten-year period with age range between 25 and 70 years with peak at 5th decade (mean 47.5 years). The male to female ratio was 1:1.7. The majority of the patients had advanced disease (TNM group stages III and IV). Palpable loin mass (89.5%), flank pain (78.9%) and visible haematuria (47.4%) were the main presenting complaints, with the classic triad seen in 47.3% of patients. Complications included anaemia, hypertension, weight loss, fever, hepatomegaly, leg swelling, cough and bone pains. The histological subtypes seen were clear cell RCC (63.2%), papillary (15.8%), chromophobe (10.5%), sarcomatoid (5.3%) and collecting duct (5.3%). Fifteen patients (78.9%) had radical nephrectomy, while in three patients (15.8%), the tumour was unresectable and inoperable in one patient. ***Conclusion:*** Renal cell carcinoma was relatively uncommon in our environment and patients presented in advanced stages with poor outcomes. Clear cell, papillary and chromophobe were the most common histological subtypes. Radical nephrectomy was the mainstay of treatment. Effective preventive measure is to avoid smoking and reduce obesity.

Keywords: Renal cell carcinoma, management, radical nephrectomy.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2-3% of all new cancers worldwide, with a global variation in incidence, western countries having a higher incidence [1]. GLOBOCAN estimates in 2022 report the global incidence were 434,840 with 155,953 deaths [2]. Renal cell carcinoma is the most common solid lesion within the kidney and accounts for 80-90% of kidney cancers, while the remainder is composed of renal pelvis cancers (about 12%) and other rare malignancies (about 2%) [2,3]. Most RCCs occur in the renal cortex which is composed of the glomerulus, tubular apparatus and collecting duct. Virtually all renal cell cancers are adenocarcinomas while the majority of renal pelvis cancers are urothelial carcinomas. RCC comprises different subtypes with different histopathological and genetic characteristics. The male to female ratio is (2:1) with peak incidence at age 60-70 years in western countries [4]. Incidence and mortality are highest in Europe and Asia, whereas the age standardised rate (ASR) is highest in North America and mortality in Eastern Europe with ASR in men 13.7/100,000 over women 6.4/100,000 respectively [1,2]. In Africa and the Middle East, the age standardized incidence for RCC is 1.8-4.8/100,000 for males and 1.2-2.2/100,000 for females respectively [1,3]. A review by Atanda and Haruna in 2017 estimated the incidence of RCC in Nigeria as approximately 0.3/100,000 population [9]. Reports from various centres in Nigeria corroborate the low incidence [7,8,9]. The rising incidence in developed countries is attributed to use of cross-sectional imaging techniques with incidental diagnoses of early-stage cancers. The morbidity and mortality of renal cancers have reduced in developed countries contrary to the situation in sub-Saharan Africa. In Nigeria and other developing countries, patients present in advanced stages, some fit for radical nephrectomy, while others present with unresectable or inoperable tumours. However, imaging techniques like CT scans and MRI are now available in several tertiary and private medical institutions in Nigeria, thus increase in the diagnoses of early-stage tumours may be expected. The aim of this

study was to determine the prevalence, age, gender distribution, presentation, histology and management of renal cell carcinoma in our centre.

PATIENTS AND METHODS

We retrospectively reviewed patients with renal cell carcinoma managed between January 2012 and December 2021 in our centre. Clinical data obtained from patients' case notes, theatre records and histopathology reports included age, gender, diagnostic investigations, stage at presentation, histology, treatment and outcome. A complete blood count, urine studies, renal function and liver function tests were done. Imaging studies included abdominopelvic and doppler ultrasound scan, chest X-Rays, Intravenous urography, CT scan and Magnetic resonance imaging (MRI). Patients who were fit for surgery had radical nephrectomy using anterior abdominal transperitoneal or retroperitoneal approaches. The resected tumours were sent for histopathology. Nineteen (I9) patients met inclusion criteria with complete data from case notes, theatre records and histopathological reports. Patients with incomplete data and histology reports were excluded. All patients were followed up for at least one year.

RESULTS

Out of the nineteen (19) patients seen, there were 7 males and 12 females giving a gender ratio (male: female of 1:1.7). The age range was 25 to 70 years with peak at 5th decade with mean age of 47.5 years. Symptoms included abdominal/flank swelling in 17 patients (89.5%), loin pain in 15 (78.9%), visible haematuria in 9 patients (47.4%), weight loss in 5 (29.4%), fever in 3 (15.8%), frequent urination in 3 (15.8%), bone pains in 2 (10.5%) and cough in 2 (10.5%), (Table 1). The major physical findings included palpable loin mass in 17 (89.5%), anaemia in 11 (57.9%), hypertension in 7 (36.8%), hepatomegaly in 3 (15.8%) and leg swelling with left varicoceles in 2 (10.5%). The classic triad of visible haematuria, flank pain and mass was present in 9 patients (47.3%).

Table 1: RCC– Clinical Presentation in 19 patients

S/N	SYMPTOM	NUMBER	%
1	Abdominal swelling	17	89.5%
2	Loin pain	15	78.9%
3	Haematuria	9	47.4%
4	Weight loss	5	29.4%
5	Fever	3	15.8%
6	Frequent urination	3	15.8%
7	Bone pains	2	10.5%
8	Cough	2	10.5%

S/N	PHYSICAL FINDINGS	NUMBER	%
1.	Loin mass	17	89.5%
2.	Anaemia	11	57.9%
3.	Hypertension	7	36.8%
4.	Hepatomegaly	3	15.8%
5.	Leg swelling + varicocele	2	10.5%
6	Pleural Effusion	1	5.3%
7	Jaundice	1	5.3%
8	Supraclavicular lymph node	1	5.3%

Diagnosis of renal cell carcinoma was made from clinical features, radiology and histopathology. Contrast enhanced CT scan demonstrated features of malignancy and enabled clinical staging (Figure 1) A majority of the patients, 16 (84.2%) had advanced disease, TNM Stage groups III and IV, while only 3 patients (15.8%) had stages I and II tumours (Table 2). Figures 1 and 2 show specimen of tumour resected at radical nephrectomy.

Fifteen patients (78.9%) had open radical nephrectomy (Table 4). In 3 patients (15.8%) the tumour was unresectable due to attachment to the liver, duodenum, colon, posterior abdominal wall and retroperitoneal structures. Three patients had ORN with tumour thrombectomy from renal vein and IVC while one patient had hepatic metastectomy. In one moribund patient who was unfit for surgery, renal core tissue needle biopsy and supraclavicular lymph node biopsy was obtained for histology. Surgical complications included primary haemorrhage, duodenal and pancreatic injury, and surgical site infection. The histological subtypes seen are shown in Table 3 while the photomicrographs are shown in Figures 4 and 5.

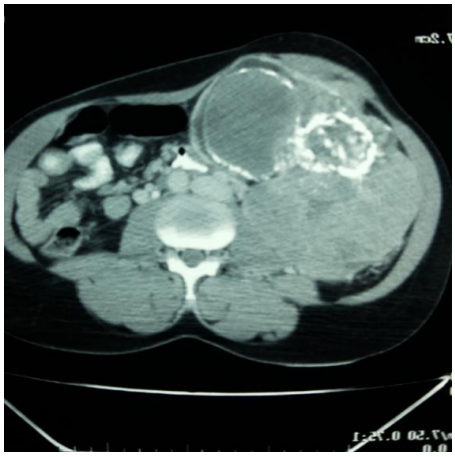

Figure 1: CT Urogram of patient with RCC

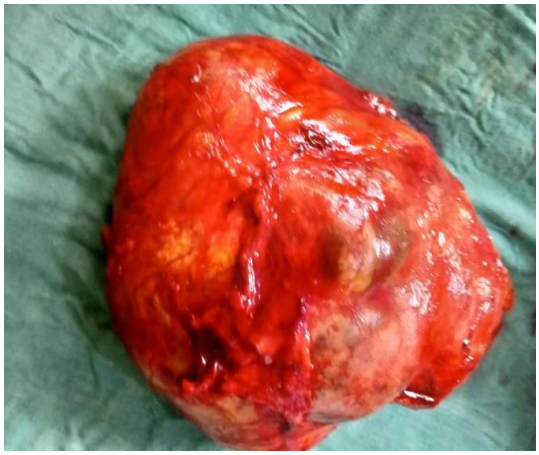

Figure 2: Radical nephrectomy specimen

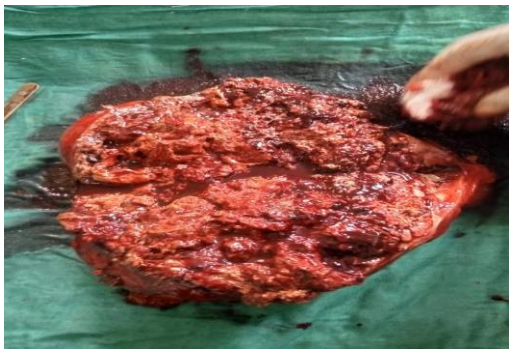

Figure 3: **RCC bivalved**

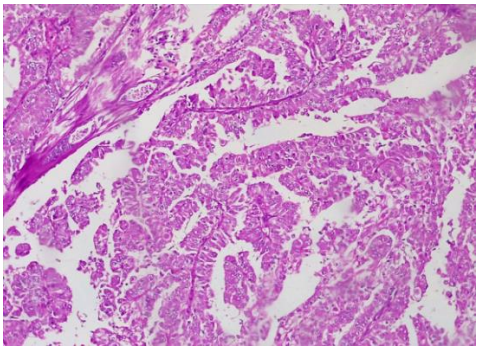

Figure 4: Papillary Renal cell carcinoma

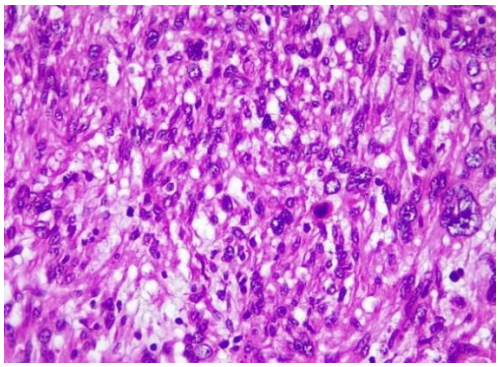

Figure 5: Sarcomatoid differentiation

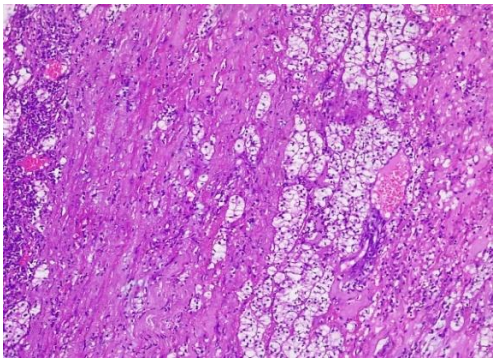

Figure 6: RCC Clear cell changes

Table 2: TNM staging (primary tumour T)

STAGE	NUMBER	PERCENTAGE
T1	1	5.5%
T2	2	10.5%
T3	6	31.6%
T4	10	52.6%
Total	19	100%

Table 3: Histological subtypes

S/N	HISTOLOGY	NUMBER	%
1	Clear cell	12	63.2%
2	Papillary	3	15.8%
3	Chromophobe	2	10.5%
4	Sarcomatoid	1	5.3%
5	Collecting duct	1	5.3%
	Total	19	100%

Table 4: Treatment Modalities

S/N	TREATMENT	NUMBER
1	Radical Nephrectomy	15
2	Medroxyprogesterone	10
3	Palliative Radiotherapy	5
4	Chemotherapy with Doxorubicin + 5 Fluro-uracil	2
5	Targeted Therapy	1

DISCUSSION

Renal cell carcinomas arise from the renal epithelium and account for approximately 2-3% of all adult cancers and approximately 90% of malignant kidney tumours in Europe and America, but it is uncommon in our environment [1,2]. It is the third most common malignancy of the genitourinary system after prostate and urinary bladder cancers. In developed countries, RCC occurs twice as often in men than in women with average age at diagnosis in the early 60s [1,2]. In our series, the age range was 25 to 70 years with peak at 5th decade, (mean 47.5 years), similar to findings in Ife (mean age 47.5), Lagos (41.8 years), and Ibadan (48 years) [8,14,20]; but earlier than in Caucasians (6th decade) [1,2]. The male to female ratio of 1:1.7 compares with studies from Ife [8] and Lagos [14]. Renal cell cancer occurs in sporadic and familial forms [2]. About two percent of cases are associated increased genetic risk [5,18]. Certain genetic and inherited syndromes associated with RCC include Von Hippel-Lindau disease, (predisposing to clear cell cancer), hereditary leiomyomatosis, hereditary papillary renal cancer (HPRC), Birt-Hogg-Dube syndrome (chromophobe and oncocytoma), chromosome 3 translocation, and tuberous sclerosis [4,5,12]. Renal medullary cancer is a rare, fatal kidney tumour that affects young blacks with sickle cell disease [9]. Having a first degree relative with kidney cancer has been associated with a 2 to 3-fold increased risk in patients with inherited syndromes [2,4]. Established modifiable exogenous risk factors include smoking, obesity, and hypertension [2,4,5]. Other associated risk factors include acquired cystic disease associated with end stage renal disease and renal transplantation, socioeconomic factors, analgesics, occupational exposure to asbestos, cadmium and petroleum products, alcohol, hormonal and reproductive factors, diabetes, metabolic syndrome, hepatitis C and radiation [1,4,5]. However, moderate alcohol intake, consumption of fruits, vegetables and carotenoids are said to be protective [6]. No significant family history or hereditary predisposition was established in our patients and genetic screening for Von Hippel-Lindau syndrome was not done. Only hypertension and antihypertensive drugs in 7 (36.8%) and smoking in 2 (10.5%) were notable predisposing factors in our patients. There was no history suggestive of prolonged exposure to gasoline, trichloroethylene, asbestos, or cadmium in this series.

Most of our patients presented with loin mass (89.5%), loin pain (78.9%), and visible haematuria (47.4%). The classic triad was seen in 9 (47.9%) patients compared to 36% in Lagos and 10%-15% often reported in developed countries. The high number of patients with local and systemic symptoms was associated with late presentation, advanced disease and poor prognosis. Other studies in Nigeria report 8-46% presentation with this triad reflecting advanced disease [8,9,12,14,15]. Fever, weight loss, bone pains, anaemia, jaundice, cough and pleural effusion were complications seen in our patients. Findings of non-emptying left varicocele and pedal oedema indicated renal vein or inferior vena cava invasion and obstruction. Systemic symptoms in renal cell carcinoma may be due to metastases or paraneoplastic events related to secreted proteins, such as renin (hypertension), erythropoietin (polycythaemia), parathyroid-hormone-related protein (hypercalcaemia), adrenocorticotropic hormone (Cushing's syndrome) and reversible hepatic dysfunction with deranged liver enzymes (Stauffer's syndrome), neuromyopathy and amyloidosis [7,13]. Paraneoplastic syndrome occurs in about 33% of patients with symptomatic RCC, but resolution occurs after radical nephrectomy. A complete blood count, coagulation profile, C-reactive protein, erythrocyte sedimentation rate, renal function tests, urine studies for proteinuria, liver enzymes including transaminases, lactate dehydrogenase, alkaline phosphatase and calcium were evaluated. Contrast enhanced CT scan is the imaging modality of choice with about 90% accuracy for renal masses and would demonstrate the tumour, renal vein and IVC invasion/thrombus, status of loco-regional lymph nodes, adrenal and hepatic extension [12,14,15,27].

Our results show that 84.2% of patients had stages T3/T4 tumours unlike findings in developed countries where over 50% of cases are early disease detected incidentally. Late hospital presentation and inadequate imaging facilities contributed to diagnosis of advanced disease in our environment. Late presentation (T3/T4) was also reported in studies from Lagos (93.7%), Ife (88.9%), Enugu and Zaria (90%) [14,15,24,26,28]. This contrasts with a report from South Africa where the most common mode of presentation was incidental finding on imaging (55%) and the median stage was pT1b, which compares with Europe and USA where 58-89% of tumours are pT1 disease less than 7cm [10]. These differences may reflect inadequate or late access to healthcare and imaging in sub–Saharan African countries, but further studies to define genetic and tumour characteristics are required [10,26].

The tumour weights ranged from 0.5 to 2.5kg and widest diameters 10cm to 21cm. Studies from other

centres in Nigeria also reported bulky tumours (weights ranging from 0.48-3.8kg and widths 15-65cm) [9,14,15], while a report from Ghana recorded tumour sizes with mean diameter of 16.8 cm [11]. Such huge tumours were either due to late presentation or tumour aggressiveness. The right kidney was affected in eleven patients (57.8%) and the left kidney in eight patients (42.1%) and tumour location was in the upper pole in 10 patients (52.6%). Clear cell cancer was predominant in 63.2%, while papillary (15.8%), chromophobe (10.5%), were common subtypes in this series. Ninety percent of RCCs are of the clear cell, papillary and chromophobe subtypes with clear cell being the most common and aggressive and the predominance of clear cell RCC has been reported in other studies [9,12,14,15].

Fifteen (15, 78.9%) patients had open radical nephrectomy. Out of these, three patients had tumour thrombectomy from renal vein and inferior vena cava, and two patients had liver nodule metastectomy. Three (3, 15.8%) patients had non-resectable tumours at operation, with tumour invading adjacent structures like colon, duodenum, liver and major vessels in the retroperitoneum. In one patient diagnosis was made by percutaneous core tissue needle biopsy and supraclavicular lymph node biopsy. These patients with advanced disease had palliative radiotherapy.

In Europe and America, 60-70% of patients have localized disease (T1/T2), detected incidentally on cross sectional imaging of the abdomen, and are suitable for nephron sparing procedures using open, laparoscopic, and robotic partial nephrectomy (PN). The goal of partial nephrectomy in early disease is to achieve local tumour control and preserve maximal renal tissue. However, about a quarter of patients in developed countries still present with advanced disease, including locally invasive or metastatic renal cell carcinoma, and a third of the patients who undergo resection of localized disease will have a recurrence [27]. Most patients in sub-Saharan Africa present with locally advanced or metastatic disease and open radical nephrectomy is treatment modality most adopted [6,7,8,12,14,15]. Radical nephrectomy involved preliminary vascular control by ligation of renal artery and vein, en-bloc removal of the kidney with tumour, perinephric fat, regional lymph nodes, upper third of the ureter and ipsilateral adrenal gland with primary dissection outside Gerota's fascia. Radical nephrectomy can be done by open, laparoscopic or robotic techniques. Routine adrenalectomy and extensive lymph node dissection is no longer recommended if abdominal CT shows no evidence of adrenal or lymph node invasion; though upper pole tumours with adrenal infiltration requires adrenalectomy. Open radical nephrectomy was the treatment modality in other Nigerian centres [8,12,14,15,20]. For large symptomatic renal tumours, ORN was executed with either curative intent or integrated into a multimodal treatment approach as cytoreductive nephrectomy for patients with metastatic disease. Immunotherapy and targeted agents have been used in the multimodal management of advanced RCC, as neoadjuvant or adjuvant therapy [6,7,13,21]. Agents for immunotherapy include interferon alpha and interleukin-2. Targeted therapeutic agents for treatment of advanced RCC include oral tyrosine kinase inhibitors (TKIs) e.g., sorafenib and sunitinib; inhibitors of mammalian target of rapamycin (mTOR) e.g., temsirolimus and everolimus; and antiangiogenic monoclonal antibody bevacizumab directed at vascular endothelial growth factor receptor (VEGFR) [21]. Systemic therapy can be used in localized and locally advanced RCC as adjuvant therapy to reduce risk of recurrence or progression or as neoadjuvant therapy to render primary renal tumours amenable to planned surgical resection [13,21]. Targeted therapies have improved progression-free survival and replaced non-specific immunotherapy with cytokines in metastatic RCC [25]. The high cost and unaffordability of these drugs in our environment make them largely unavailable to our patients [26]. A few studies in Nigeria have documented the use of these agents in advanced metastatic disease (Salako [8] Tijani [14] and Muhammed [28]). In the Zaria study, four patients (7.8%) who had adjuvant treatment with immunotherapy or vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitors had a better prognosis [28]. Median survival for patients with metastatic disease is about 13 months, thus there is need for more effective surgical and medical therapies [4]. RCC expresses glycoprotein P, thus is chemoresistant. However, chemotherapeutic agents including gemcitabine and doxorubicin or capecitabine have been used in non-clear (sarcomatoid) RCC [7] and two of our patients with sarcomatoid RCC were given doxorubicin and 5-Fluorouracil. Renal cell cancer is traditionally radioresistant, though indications for adjuvant radiotherapy may include positive surgical margins, perinephric fat or adrenal gland invasion, regional lymph node involvement, unresectable tumours and palliation of bone metastases [7,17]. Modern techniques of stereotactic body radiotherapy (SBRT) may have a role in the treatment of cancer in solitary kidney or bilateral RCC [7].

Clear cell RCC had a worse prognosis compared with papillary and chromophobe tumours. Sarcomatoid differentiation had aggressive local and metastatic behaviour and poor prognosis. Three patients (15.9%) with T1/T2 tumours were alive 5 years after surgery, while patients with T3/T4 and metastatic disease were lost to follow-up or not alive after 48 months. The patients with unresectable tumours died within 6 months. The poor outcome is similar to findings from other centres in the subregion and is attributable to late presentation and inadequate access to diagnostic facilities [8,9,14,15,22,26,28].

CONCLUSION

Renal cell carcinoma in our environment was commoner in females, presenting in advanced stages.

Clear cell, papillary and chromophobe RCC were the predominant histological subtypes. In our environment, the most important prognostic factor was resectability. Open radical nephrectomy was the most widely adopted treatment modality due to its practicability, cost effectiveness and applicability at various stages.

RECOMMENDATIONS

Advances in management of RCC requires a multidisciplinary approach with early imaging and staging; evolving treatment strategies including open, laparoscopic or robotic partial nephrectomy, radical nephrectomy, cytoreductive nephrectomy, immunotherapy and systemic targeted therapy. Availability and affordability of targeted therapeutic agents for advanced cases may improve the prognosis. Prevention is by avoiding lifestyle risk factors like smoking, obesity, hypertension and metabolic syndrome.

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