



The Continued Burden of Renal Cell Carcinoma in a Developing Country. Lessons Learnt or Not Learnt?

**F. O. Ugwumba^{1*}, O. C. Okafor², I. I. Nnabugwu¹, K. N. Echeta¹, A. D. Okoh¹,
E. F. Nnakenyi² and E. I. Udeh¹**

¹*Urology Unit, Department of Surgery, University of Nigeria Teaching Hospital, Enugu State, Nigeria.*

²*Department of Morbid Anatomy, University of Nigeria Teaching Hospital, Enugu State, Nigeria.*

Authors' contributions

This work was carried out in collaboration between all authors. Authors FOU and OCO designed the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Authors IIN, KNE and ADO reviewed the analysis and contributed to subsequent drafts. Authors EFN and EIU managed the literature searches, reviewed analysis and contributed to drafts. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the incidence, gender distribution, presentation, management, histopathological features and outcome of renal cell carcinoma (RCC).

Study Design: Retrospective study.

Place and Duration of Study: University of Nigeria Teaching Hospital, Saint Mary's Hospital, Royal Hospital, Mother of Christ Specialist Hospital and Eastside Hospital between January 2002 and December 2015.

Methodology: We included 54 patients (29 men, 25 women; age range 19–67 years). Information abstracted included age, gender, presenting symptoms, imaging modality used, clinical stage of the disease and other relevant laboratory results. Histopathology results, duration of follow up, clinical outcome, use of targeted therapies and their duration.

Results: The mean age was 37.61 ± 15.1 years Tumours were most frequent in the 4th decade of life, the male: female ratio was 1.16: 1. Smoking and obesity as risk factors were present in 7 patients (all male) and 2 patients respectively; familial-related RCC, as well as VHL-related RCC or

*Corresponding author: E-mail: fredugwumba@gmail.com;

long term dialysis-related RCC were absent. Loin mass in 54 patients (100%) and loin pain in 50 patients (92.5%) were the more common presentations. Right-sided tumours were slightly more common (28 patients, 51%).

Late presentation was the bane, with onset-presentation interval being 3–34 months (mean 10). Commonest imaging modality was ultrasound (54 patients, 100%); intravenous urography (30 patients, 55.5%), and CT urography/ abdomen (24 patients, 44.4%). 8 patients were managed non-operatively, while 46 patients (85.2%) had radical nephrectomy. Clear cell and papillary carcinoma were the histologic patterns seen in 43/46 patients (93.4%) and 3/46 patients (6.5%) respectively. Follow up was short, mean 7 months (range 4-46 months).

Conclusion: Late presentation, paucity of radiotherapy services, short duration of follow-up and prohibitive costs of targeted therapies were challenging.

We recommend enlightenment and strengthening of the health system aimed at earlier detection.

Keywords: Renal cell carcinoma; burden; Nigeria; developing country.

1. INTRODUCTION

The incidence of renal cell carcinoma (RCC) in the United States of America has risen consistently in the last decade with a total of 342,501 RCC cases being diagnosed [1]. The RCC incidence rate increased from 10.6/100,000 individuals in 2001 to 12.4/100,000 in 2010 with a M; F ratio of 2:1. The annual percent change was higher in women than in men and in those 20 to 24 years old [1].

In Europe, similarly high incidence rates have also been observed recently at 17.2/100,000 for male and 8.1/100,000 for female and mortality rates of 7.2 and 2.8/100,000 for males and females respectively [2]. Despite these increasing incidence rates, there is an accompanying reduction in tumour size at diagnosis, and improved survival in this category of patients [3]. This picture is probably attributable to earlier detection and treatment, occasioned by better health care systems, access and affordability of care. The picture in West Africa has been markedly different, with reports showing that up to 80% of patients present with high stage tumours, with consequent poor prognostic outcomes [4-7].

Risk factors associated with RCC include cigarette smoking, obesity, occupational exposure and the genetically inherited syndromes associated with RCC.

Of these factors, obesity and cigarette smoking are on the rise in developing countries [8,9]. These present targets for lifestyle modification and potential cancer reduction [10,11].

The mainstay of treatment of early stage renal cell carcinoma is surgical extirpation, but the

current therapies for metastatic RCC such as the anti-vascular endothelial growth factor agent (VEGF) bevacizumab, mammalian target of rapamycin inhibitors (mTOR) e.g. temsirolimus and interferon alpha where available, are often prohibitively expensive for most patients in our setting. Previous workers have estimated the lifetime costs of these targeted agents, such as bevacizumab, sunitinib, sorafenib and temsirolimus, to be up to (\$US8, 537-\$72, 254) [12].

Given the foregoing, and the observations of earlier authors regarding high stage at diagnosis and late presentation, we conducted this study to assess the incidence, gender distribution, presentation, management, histopathological features and outcome of RCC in Enugu Nigeria, and to determine if any changes in the previous trends have occurred.

Our study setting was Enugu in South East Nigeria, at five locations; the University of Nigeria Teaching Hospital and other 4 other hospitals where urology services are provided. Enugu has an estimated population of 3,800,000 people as at the 2006 census, [13] and also receives patients from the neighbouring states of Abia, Anambra, Imo Ebonyi Rivers Benue and Kogi States with a combined population of over 20 million people [14].

2. MATERIALS AND METHODS

Over a thirteen year period from January 2002 to December 2015, 54 out of 69 patients with adequate information that were treated for renal cell carcinoma in four hospitals, namely University of Nigeria Teaching Hospital, Saint Mary's Hospital, Royal Hospital, Mother of Christ Specialist Hospital

and Eastside Hospital all in Enugu were identified from personal surgeons logs, clinic, ward admission and operating theatre records. Relevant information was collected using a data abstraction form.

Information abstracted included age, gender, presenting symptoms, imaging modality used (ultrasound, chest X-ray, computerized tomography), clinical stage of the disease and other relevant laboratory results.

Operation notes were reviewed for intraoperative findings (renal cortex breach, gerota fascia breach, lymph node involvement and renal vein / IVC involvement and type of operation performed.

Other findings noted were histopathology results, duration of follow up, clinical outcome, and use of targeted therapies.

2.1 Statistical Analysis

Results were subjected to statistical analysis using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). Demographic data were analyzed as frequencies and percentages. Categorical data were analysed using the Chi square test with significance level set as $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1 Results

Results of the 54 patients seen during the study duration, mean age was 37.61 ± 15.1 (range 19–67 years). Tumours were most commonly seen in the 4th decade of life. Male; female ratio was 1.12:1.

Concerning risk factors, prior history of smoking was seen in 7 male patients. There was no family history of RCC, Von Hippel Lindau syndrome or long term haemodialysis. Obesity was present in 2 patients.

The more common presentations seen were loin mass in 54 patients (100%) and loin pain in 50 patients (92.5). (Table 1) Concerning laterality, 28 patients (51%) had right-sided tumours while 26 patients (43%) were left-sided. No bilateral case was seen.

Onset-presentation interval was 3-34 months, mean 10 months. Imaging modality for diagnosis

was ultrasonography in all 54(100%), intravenous urography in 30 patients (55.5%), and computerized tomography (CT) in 24 patients (44.4%).

Table 1. Clinical presentation of renal cell carcinoma seen

Symptom/Sign	N	%
Asymptomatic	1	1.85
Loin mass	54	100
Loin pain	50	92.6
Haematuria	26	48.1
Triad of Symptoms (loin mass, loin pain and haematuria)	19	35.2
Weight loss	43	79.6
Malaise	41	75.9
Anaemia	41	75.9
Fever	11	20.4
Cough	4	7.4
Varicocoele	6	11.1
Supraclavicular lymph nodes	4	7.4

Concerning treatment, 46 (85.2%) patients had radical nephrectomy, while 8 (14.8%) were managed non-operatively. Molecular targeted therapy was used incompletely in 3 patients. Concerning clinical tumour staging (TNM), the most frequently seen stage was T3 (Table 2).

Table 2. TNM clinical staging in 46 operated cases

Stage	N	%
T1	1	2.20
T2b	8	17.39
T3a	19	41.30
T3b	5	10.87
T4	13	28.26
Total	46	100%

Histologic pattern seen was clear cell in 43/46 patients (93.4%) and papillary in 3/46 patients (6.5%). Relevant operative findings in our series were large tumour size mean 24 cm (15 to 38 cm), adrenal gland and lymph node involvement, renal vein and vena cava extension.

3/46 patients (6.5%) had level 1 inferior vena cava thrombectomy.

Significant complications observed were primary haemorrhage in 3/46 patients, pulmonary embolism in 2/46, splenic/pancreatic injury in 1/46 each.

Duration of follow up was 4-46 month with a mean of 7 months. At 4 months after surgery, 7/46(15.2%) had been lost to follow up. 8/46(17.4%) patients re-presented between 6 and 19 months after surgery with evidence of metastatic disease or local recurrence and died. Mortality was 2/46 (4.3%) at one month after surgery. Of the 21/26 patients followed up for 2years, a chi-square test of independence was performed to examine the relationship between tumour stage and survival. The relationship between these variables was significant. $P < 0.05$ (Fishers exact test)

3.2 Discussion

Within the 13 year study period, 54 patients were seen, about 5 / year, this is slightly lower than the 74 cases reported previously in our city [4]. The reason for this difference is not known but may be due to an increase in the number of health care facilities able to offer treatment for this condition in the vicinity.

The mean age incidence was 37.61 ± 15.1 (range 19–67 years). Peak age incidence was in the 4th decade of life. Male: female ratio was 1.12:1, this is similar to the findings of previous authors [4-7] that reported the highest frequency of cases in the 4th decade. Noteworthy though, is that our series had a mean age incidence in the 4th decade. This contrasts with the findings in the United States [1,3].

Reasons for this may be the obvious youth demographic bulge, with 69.1% of the population being under 30 years old, [13] and the lower life expectancy in Nigeria [14]. The male to female ratio observed showed a male predominance which is in keeping with the findings of previous workers in the United States [1,3] and developing countries [4,5] although reversals of this pattern have been reported [15].

Regarding risk factors, there were no cases of VHL syndrome or long term treatment renal replacement therapy with haemodialysis. We did not elicit any history of aniline dye exposure or family history of RCC. Positive smoking history of between 5-17 years was elicited in 7/54 (12.9%) of the male patients, while obesity was noted in 2/54(3.7%) It has been shown that while both cigarette smoking and obesity are independent risk factors for renal cell carcinoma, cigarette smoking in addition increases the risk of advanced RCC [16-18]. While these factors

appear to account for a minority of cases they remain targets for lifestyle modification that may mitigate the risk in our setting.

There was one incidentally discovered tumour (1.85%). This is a far cry from the paradigm in the western world where majority of the tumours are diagnosed in the course of abdominal imaging for other conditions [1,2,3].

Onset presentation interval was 3-34 months mean 10 months. In other climes where outcomes are better, the norm is to have the majority of the cases screen detected or diagnosed early. This has not been the case in our experience and those of others in our sub-region who have recorded similarly long intervals between onset and presentation [4-7,15,19]. This observation, is probably multifactorial and may be due to poor access to care, ignorance and weak health care systems amongst others.

Loin mass, loin pain and haematuria were seen in 54 (100%), 50 (92.5%) and 26 (48.1%) patients respectively. Triad of symptoms (loin mass, loin pain and haematuria were seen in 19 patients (35.2%). Sadly, this pattern of presentation appears to be the norm in our climes as has been reported often by authors across many countries with similar development indices [4-7,13,14] in West Africa. Comparatively in the Middle East, up to 26% of tumours are reported to be incidentally discovered, [20] with similar findings in the United States. These are associated with improved outcomes.

The possible contributory factors leading to this situation are many and include poorly developed primary care system for early assessment and referrals, poverty, ignorance, patronage of alternative medicine practitioners and faith healers [21,22,23]. Late symptoms/signs such as weight loss and malaise which was seen in 43/54(79.6) and 41/54(75.9%) of patients were often the main triggers to presentation and is emblematic of the late presentation challenge. Anaemia which occurred in 41/54(75.9%), remained a consistent feature of delayed presentation as observed by Aghaji et al. (66.2%) and Avakoudjo et al. (67.7%) in earlier series. [4,19].

Imaging studies used in the confirmation of clinical diagnosis was ultrasonography in all 54(100%), IVU in 30(55.5%), CT urography/abdomen 24(44.4%). This usage pattern of imaging studies was due to the near

universal availability of ultrasound and relatively affordability. This is in agreement with earlier studies [4,5]. Intravenous urography was done in addition to ultrasound in 30 patients (55.5%), that were mostly seen during the early part of the study, again due to ease of access and lower costs than CT scanning.

Previously, in most parts of Sub-Saharan Africa access to CT had been limited by prohibitive cost and distance, [24] over time, however, the availability and uptake of CT scanning has risen [15], and with it, the ability to diagnose and stage malignant renal lesions with a high degree of accuracy [25].

As a result of these factors CT urography has become a more used, and our preferred imaging option for RCC as it allows excellent cross sectional imaging and staging as well as assessment of the functional status of the contralateral kidney.

3.3 Treatment

The treatment paradigm for renal cell carcinoma has remained radical nephrectomy (RN) where possible, [26] this is based on the relative resistance of the tumour to chemotherapy and radiotherapy [15,27] Operative intervention was done as RN in 46 patients. Some pertinent operative findings in our series were large tumour size, adrenal gland and, lymph node involvement, renal vein and inferior vena cava extension of tumour. These essentially mirror results from other centres in the region. [4,5,6].

Of these 46 patients, the commonly observed complication for the T3 and > tumours, were intraoperative haemorrhage pulmonary embolism and adjacent organ injury. 30 day mortality was 2/46 (4.35%) in the series. These mortalities were due to significant post-operative haemorrhage.

8/54 patients were too ill to undergo surgery and had to be managed non-operatively. This was due to presentation as advanced disease. Similar observations have been made by other authors in Nigeria, Benin Republic and Senegal [4,5,13,14] The modern surgical trend is towards nephron sparing and minimally invasive surgery via the laparoscopic or retroperitoneoscopic routes with clearly demonstrable advantages [28] Given the peculiar health

system challenges highlighted earlier, perhaps efforts are better geared towards ensuring improved access and earlier detection for the majority of persons.

Concerning systemic targeted therapy, these are associated with prohibitive costs [12] which has been shown to be unaffordable to the majority of patients [13].

We noted great funding challenges in the patients with metastatic disease that required palliation, only one was able to afford 2 doses. This resulted in the situation where palliation was restricted chemotherapy and to erratically available radiotherapy and in some cases only analgesics and supportive care. Omoruyi et al, [29] have painted a vivid picture of the suboptimal, overworked radiotherapy facilities in Nigeria, attended by frequent equipment failure and long periods of downtime which often result in patients being unable to access the needed care in a timely manner.

Of the 46 operated patients who had radical nephrectomy, the commonest histologic pattern was clear cell carcinoma which was seen in 93.4% of cases, This is in agreement with other findings from West Africa [4-7,13,14] and globally [3,30].

Follow up duration was poor and ranged from 4-46 months with a mean of 7 months and is similar to previous findings in the sub-region [4,5,15].

8/46 (17.4%) patients re-presented between 6-19 months after surgery with a variety of features of local recurrence and metastatic disease such as abdominal masses, malignant ascites, liver metastases and pleural effusion. These were likely due to the high stage at presentation and inadequate adjuvant or systemic therapy. These recurrences occurring usually within 1 year of surgery have been observed by other authors previously [31]. The 3 patients that were followed up for up to >3years remained recurrence/symptom free and all had stage 1 or 2 tumours at presentation as has been observed previously [4].

There was a statistically significant difference in survival at 2 years by TNM stage with the higher stage lesions having worse outcome, as has been shown previously [4,5,19].

4. CONCLUSION

While the hospital incidence of RCC has remained stable with a slight male predominance, challenges that continue to be encountered are late presentation and high stage at presentation, paucity of funds to access modern imaging in some cases, high cost of surgical care and prohibitive cost of targeted therapies where required. Access to regularly functioning radiotherapy services also remains difficult.

A systematic broad based approach that involves improved patient education and strengthening of primary healthcare services may allow earlier detection and consequent improvement in outcome.

The inclusion of an annual abdominal ultrasonographic scan as part of the annual physical examination is suggested as a low cost measure with potential benefit in early detection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was approved by the University of Nigeria Hospital Research Ethics Committee; approval number NHREC/05/01/2008B/UNTH/CSA.329/Vol.6.

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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