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Adult renal cell carcinoma in Lagos: Experience and challenges at the Lagos University Teaching Hospital

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Abstract
Introduction: Renal cell carcinoma (RCC), regarded as the most lethal of all urological tumors, is relatively uncommon. Recent reports from developed countries indicate a rising incidence, most likely from the increasing availability of imaging services leading to an increase in incidental diagnosis of early stage tumors, with consequently better prognosis. However, literature on RCC in sub-Saharan Africa is relatively sparse.
Objectives: To determine the prevalence, presentation, pattern and outcome of RCC at the Lagos University Teaching Hospital.
Methods: Information extracted from the records of 64 adult patients with RCC seen in our institution between January 2000 and December 2010 included the age and sex of the patient, clinical features, investigations, tumor stage, treatment, outcome of management and follow-up.
Results: The mean patient age was 41.8 years (range 20–75 years) with a male:female ratio of 1:1.7. Flank mass, flank pain and hematuria were present in 90.6%, 86% and 40.6% of patients, respectively, while 36% of patients had the classical triad of loin pain, loin mass and hematuria. Only 1 patient (1.6%) had an incidental diagnosis. TNM tumor stages T3 and T4 accounted for 93.7% of patients, while the clear cell type accounted for 60% of histologically examined cases. Forty-five patients (70.3%) had surgical intervention. Of the T2 patients available for follow-up, 50% were alive at 48 months, while all inoperable T4 and M1 patients available for follow-up were dead within 1 year.

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Conclusion: RCC in our environment is characterized by a younger age at presentation, a female predominance and clinical presentation at an advanced clinical stage.

Introduction

Recent reports from developed countries indicate a rising incidence of renal cell carcinoma (RCC), most likely from the increasing availability of imaging services leading to an increase in incidental diagnoses [1]. RCC is a relatively uncommon malignancy in Nigeria; while the world wide incidence is about 3.9/100.000 [2]. It is said to be rare in Africans and Asians, and accounts for more than 31.000 new cases annually in the United States [3]. Earlier reports by Lawani et al. in 1982 indicated that RCC accounted for 20.9% of all urogenital tumors in Nigeria [4], whereas Klufio recently reported that it accounted for 10.4% of all urogenital tumors in Ghana [5]. In most developed countries, the evaluation and management of RCC has evolved in recent decades in response to the changing clinical presentation of the disease. Traditionally, patients with RCC presented with signs or symptoms and the disease was usually locally advanced and often metastatic, with a poor prognosis. In 1973 only 13% of cases in the USA were diagnosed incidentally, compared to 61% in 1998 [6]. With increasing use of axial body imaging in the evaluation of nonspecific abdominal complaints, currently more than 70% of RCC cases are diagnosed incidentally, with consequent stage migration toward smaller, organ-confined tumors appropriate for nephron-sparing approaches, with the more favorable outcome [7,8]. In contrast, earlier reports from Nigeria and other parts of Africa indicated that these tumors were often diagnosed in advanced stages because patients presented when they were moribund or unfit for surgical intervention, with consequently poor prognosis even after nephrectomy [9–11].

The present study was carried out at Lagos University Teaching Hospital Idi-Araba, which provides specialized health care for Lagos state, with 15 million residents and referrals from various parts of Nigeria. It was undertaken to determine the prevalence, age, sex distribution, current pattern of presentation, histological variants, management and treatment outcome of RCC in the Lagos metropolis, and to compare the findings with other reports on this disease.

Materials and methods

Between January 2000 and December 2010, 64 adults with RCC seen in our institution were managed and followed up. Information extracted from the patients' records and analyzed included the age, sex, clinical features, investigations, histological variants, stage of the disease, treatment options, outcome of management and follow-up. All patients were evaluated with at least an ultrasound scan, computerized tomographic (CT) scan and chest X-ray. Other investigations that were performed when indicated (and available) included magnetic resonance imaging and image guided fine needle aspiration cytology (FNAC). All patients that qualified for surgical intervention were operated via a transperitoneal approach. A preliminary exploration was done to assess operability and confirm preoperative findings.

All histology and cytology slides were reviewed by a single pathologist (CCA). Hematoxylin and eosin (H&E) stained slides were retrieved from the archives and where necessary new slides were made from stored paraffin embedded tissue blocks. Faded slides were re-stained and all slides were reviewed and diagnosis modified as appropriate. The tumors were classified according to the WHO classification of 2003 [12].

Follow-up was patient specific. As a rule, all patients who had undergone radical nephrectomy (RN) were scheduled to be followed up every 3 months for at least 1 year with reducing frequency later. Follow-up included disease related history, examination and routine ultrasound at 6 months for patients without problems.

Results

The mean patient age was 41.8 years (range 20–75 years), the peak age incidence was the 5th decade, followed by the 3rd decade. The male to female ratio was 1:1.7. Only 1 patient (1.6%) had a family history of malignant renal tumor (mother) while 3 (4.7%) had exposure to industrial dyes. A history of tobacco use ranging from 2 to 15 years was obtained in 7 patients (11%). Clinical presentation included hematuria in 26 patients (40.6%), loin pain in 55 (86%), a palpable flank mass in 58 (90.6%) and the triad of hematuria, flank pain and palpable mass in 23 (36%) patients. Hematuria was the first symptom in 16 patients (25%). Only 1 patient (1.6%) was asymptomatic and had the tumor detected during abdominal imaging for unrelated symptoms. The tumor was located on the right side in 31 patients (48.4%), on the left side in 28 (43.8%) and bilaterally in 5 (7.8%).

There was history of weight loss in 35 patients (54.7%) and 15 (23%) were febrile at presentation. Anemia was present in 42.3%, night sweats in 7.7%, pedal oedema in 10 (15.6%) and 2 of 24 male patients (8.3%) had an irreducible varicocele (one on the right and one on the left side). The time from onset of symptoms to the clinical diagnosis of RCC ranged from one week to four years (average 12 months).

The diagnosis of RCC was made on clinical features and CT findings of a contrast enhancing solid renal mass in all patients. The diagnosis was confirmed on histology from an operative specimen in 45 patients (70.3%), on FNAC in 11 (17.2%) patients with clinically advanced and inoperable disease, and on clinical and radiological findings alone in 8 (12.5%) patients with clinically advanced and inoperable tumors.

Clear cell carcinoma accounted for 27 (60%) of the 45 patients with histopathology while the papillary subtype accounted for 12 (26.7%). Females accounted for 63% and 67% of the clear cell and papillary tumors, respectively. Collecting duct, sarcomatoid and chromophobe types accounted for 4 (8.9%), 1 (2.2%) and 1 (2.2%), respectively. Seven of the 11 cases confirmed with FNAC

were characterized as clear cell type while the remaining 4 could not be characterized.

The clinical tumor stage was T2 in 4 (6.3%), T3 in 39 (60.9%) – T3a in 30 (46.9%), T3b in 7 (10.9%), T3c in 2 (3.1%) – and T4 in 21 (32.8%) of cases. There was clinical or radiological evidence of regional lymph node enlargement in 33 (51%) and distant metastasis in 23 patients (36%).

The treatment in 45 (70.3%) of the patients was surgery. In 4 of these patients the tumor was reported as inoperable because of infiltration into the surrounding structures, including the liver and posterior abdominal wall. In these patients only tissue sampling was performed, while the others underwent RN. Operative mortality was 6.3%—two patients died from excessive hemorrhage while one patient with vena cava thrombus died from massive pulmonary embolism. The mean diameter of the tumor removed was 22 cm (range 12–30 cm). Major post-operative complications included intra-abdominal bleeding necessitating re-exploration, wound infection, bowel injury, pancreatic injury, septicemia, and subacute intestinal obstruction. The remaining 19 patients were managed non-operatively and referred to the oncology department. Main treatment offered included bevacizumab (avastin) in combination with interferon alpha (if affordable) and other palliative measures including radiotherapy.

Average follow-up was 10 months (range 3–52 months) and 42 (67%) patients were lost to follow-up. Among the patients with T2 tumors, 2 were alive at 4 years, 1 presented 12 months after RN with metastases and died within a year while 1 was lost to follow-up after 12 months after RN. All the inoperable T4 and M1 patients available for follow-up were dead in less than 1 year.

Discussion

RCC is relatively uncommon and is reported to account for about 2–3% of all adult cancers and 85% of all malignant kidney tumors in Europe and America [3]. The biopsy records of the Department of Morbid Anatomy of our hospital showed that RCC accounted for only 3.7% of all urogenital tumors during the period of study. This is in contrast to an earlier study from Ghana, which reported a prevalence of about 10.4% of all urogenital tumors [5]. The reasons for this are not clear. Possible explanations may include the recent increase in the diagnosis of prostate and cervical cancer as a result of screening programs. Another possible explanation may be that a patient with advanced RCC who is not fit for surgery may escape tissue diagnosis, as was the case in 12.5% of the patients in this study.

RCC was almost twice as common in females than males (M:F ratio 1:1.7). This is contrary to most reports in the literature which indicate a male predominance [2]. The peak age of incidence in our study was the 5th decade, which is similar to findings in other studies in our environment and is at least one decade earlier than figures reported in literature for Caucasians [2]. The second highest incidence in this study was the 3rd decade. There is no clear explanation for this. The average life expectancy of about 48 years in Nigeria [13] may be a contributory factor, as there is a low proportion of elderly people in the population.

The majority of the patients in this study did not have any of the known predisposing factors for RCC. Even though tobacco smoking is the only generally accepted environmental risk factor, only 5 (7.8%) of the patients gave a history of cigarette smoking of 3 years or more.

Whereas in developed countries most cases of RCC are diagnosed incidentally on imaging, with consequently earlier stage at diagnosis [7,8,14,15], only 1 patient in our study had an incidental diagnosis. Indeed, over 90% of the patients presented with Robson stage 3 or 4 disease, similar to the experience of others in sub-Saharan Africa [16]. This perhaps constitutes the greatest impediment to effective therapy in our environment. Patients often present with apparently early stage disease, but after being informed of the need for surgery, default with the aim of seeking alternate therapy with traditional (alternative) health practitioners. These patients tend to present many months or years later with incurable disease, as was the case with 7 patients in this study. Poverty and ignorance are contributory factors, as is the practice of some general practitioners who simply prescribe antibiotics or anti-schistosomal drugs for patients with hematuria, rather than to fully evaluate them. All the patients except 1 in this study who had hematuria as their first symptom were treated with an antibiotic or anti-schistosomal drug without any imaging requested by the first attending physician.

In this study hematuria (40.6%), flank pain (86%) and flank mass (91.6%) were prominent symptoms of RCC. This "classical triad", which often indicates incurable disease, is said to occur in less than 10% of patients in more developed countries [17] but was found in 36% of our patients. In developed countries hematuria is the commonest symptom of RCC, whereas in our study loin pain and loin mass were twice as common as hematuria, similar to the findings of others in our environment [11,16]. However, in patients who had hematuria, it was the earliest symptom in 62%. Significant weight loss (50%) and severe anemia (42.3%) seen in these patients were suggestive of advanced disease at presentation. Varicocele was present in 2 (8.3%) of 24 male patients, thus it is not a common feature of RCC in our environment.

Histological diagnosis was available in 70.3% of the patients who had surgical intervention while cytological diagnosis was available in 17.2%. Even though the role of FNAC in the management of RCC is limited, it is useful in confirming the diagnosis in patients with advanced disease not fit for surgical intervention. It is possible to identify the clear cell variant because the characteristics of the cells are visible on cytology, as was the case in 7 patients in this study. For the remaining 12.5% the diagnosis was based on clinical and radiological findings alone. These patients presented with locally advanced and metastatic disease. Ideally, tissue diagnosis is regarded as the gold standard for the diagnosis of malignancy. However, even in asymptomatic RCC patients, modern cross-sectional imaging techniques are so accurate that false positive diagnoses are uncommon [18]. In all the patients without tissue diagnosis in this study the CT scan showed a contrast enhancing solid renal mass in addition to both radiological and clinical features of well-advanced malignant disease.

RCC is relatively resistant to radiotherapy and other forms of systemic therapy, therefore surgical excision is the mainstay of treatment. For patients with operable tumors the treatment of choice is RN, with removal of the diseased kidney outside of Gerota's fascia and adrenalectomy if the gland is involved. In this study, the mean diameter of tumor removed was 22 cm. This contrasts with reports from developed countries with an average of 5–8 cm,

but is consistent with the findings of Badmus et al. in Southwest Nigeria [16]. Even though the current trend is toward nephron-sparing and laparoscopic surgery, our patient characteristics and the endemic infrastructural challenges make these options unrealistic. Operative mortality in this study was 6.3%. This is higher than the 2.8% quoted in Western literature [19]. The late presentation by patients in our environment may be responsible for this higher mortality. Even though controversial, in our center RN is offered to all RCC patients who are regarded as operable on imaging and considered fit for surgery, irrespective of the clinical stage. We have found this useful in temporary symptom palliation. Likewise, patients with apparently resectable T3 tumors with metastases deemed too ill to undergo surgery were excluded from surgical intervention. Even though T3b and T3c accounted for only 14.1% of all tumors, there was radiological evidence of venous involvement in at least 25% of all patients. Tumor thrombi with minimal IVC extension were removed via the incision at the ostium of the renal vein. Due to technical and infrastructural limitations we were not able to offer surgery for patients with extensive IVC involvement. Two patients died from excessive hemorrhage, while 1 patient died from massive pulmonary embolism. Two of these 3 patients had T3b tumors.

Over the past 2 decades, the histological classification of RCC has undergone significant changes. We have adopted the WHO classification [12]. Clear cell RCC accounted for a majority of cases (about 60%), followed by the papillary sub-type (26.6%). This is consistent with reports in the literature, even though most studies had given figures of about 70–80% for clear cell and 10–15% for papillary RCC [15,20]. Females accounted for the majority among all histological groups. The reason for the relatively lower prevalence of clear cell RCC in this study is unclear. However, in an earlier review of patients with renal tumors by Badmus et al. in Ife, South-west Nigeria, the clear cell type accounted for only 46.2% of all cases RCC [16].

RCC is relatively resistant to chemotherapy and radiotherapy. However, this was the principal method of palliative management available for patients with advanced disease. Unfortunately, very few patients were able to afford bevacizumab (avastin) and interferon alpha, the main forms of therapy available in our environment.

Follow-up in this study was very poor, with 67% of patients lost to follow-up, thereby making accurate conclusions on prognosis impossible. This is not unusual, because of the lack of good follow-up support infrastructure in our environment, such as transport and communication. Our patients often travel long distances to obtain specialist care and are totally responsible for the cost of their medical care. As in most other reports, tumor stage was the most important prognostic factor. All the patients with T4 and M1 tumors available for follow-up were dead within 12 months, while 50% of those with T2 tumors were alive at 48 months. The patient who had a distant recurrence one year after RN for a T2 tumor had a collecting duct histological type.

In conclusion, patients with RCC in our environment are more likely to be females, tend to present at an earlier age, but with late stage disease and a subsequently poor prognosis. The clear cell variant accounted for 60% of cases. Continuing medical education with special emphasis to increase the awareness of general medical practitioners on the need for a thorough urological evaluation of patients presenting with any form of hematuria, is recommended.

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