RENAL CELL CARCINOMA PRESENTATION AND TREATMENT

Abdalla M. Etabbal, Younis M. Al Bashari, Khalid M. Darzz, Mohamed A. El Ayan

Department of Urology Center and Benghazi Medical Center, Benghazi-Libya Faculty Of Medicine, Benghazi University

ABSTRACT

RCC is the most lethal of common urologic cancers; it is the most frequently occurring solid lesion within the kidney and comprises different types with specific histopathological characteristics for each. By using different diagnostic tools and advancement of imaging techniques there is an increase in the number of incidentally discovered renal tumors, these tumors are smaller and of lower stage. However, Current radiologic techniques of CT, US, or MRI do not distinguish histologic subtype of small renal cortical neoplasms. Despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence. The aim of this study is to evaluate the cases of renal cell carcinoma regarding the age and sex of patients presented with renal tumor, symptoms at the time of presentation, physical findings, results of laboratory investigations, imaging study results and complications of surgery as well as histopathological results. The study was performed by reviewing 23 patient's files of renal mass who admitted to urology center in the period from Aug 2009 to Aug 2014. Out of 23 cases of RCC, approximate 61% were males and 39% were females of different age groups with the mean age 59 years and the ratio of male to female is 1.6:1. However, the peak incidence of occurring RCC between 50-70 years of age and represents approximately 52% of all cases. The most common presenting symptoms were flank pain with or without other urological symptoms and accounts about 48% of all cases and hematuria with or without other urological symptoms recorded in about 39% of cases, however, about 30% of cases were discovered incidentally and considered as the third most common presenting figure of disease. On physical examination there were no obvious abnormal physical findings in about 52% cases, while in about 39% cases the tumor was palpable. Laboratory results was normal in about 43% of patients. However, about 35% of patients were anemic, while ESR was high in about 30% of patients. The imaging studies disclosed right side renal tumor in 43% patients and left side renal tumor in 48% of patients while bilateral renal tumors detected in about 9 % of cases. The size of the tumor was less than 7 cm in average diameter in 60% of patients while in 40% of patients the tumors size was more than 7 cm in average diameter. The sites of renal tumor were at upper in 56% of cases, at mid portion in 4% of cases, at lower pole in 28% of cases while the tumor was diffuse in 12% of cases. The histopathological results of resected renal masses as follow conventional (clear-cell) cell carcinoma in 50% of cases, papillary-cell carcinoma in 15% of cases Chromophobe-cell carcinoma 5% of cases. However, Unclassified-cell carcinoma found in 30% of cases. The widespread use of abdominal computed tomography and ultrasonography during the diagnostic imaging of nonspecific abdominal complaints has led to the increased detection of incidental small renal masses causing no obvious symptoms. Surgical resection still remains the only effective treatment, however, local recurrence without evidence of metastatic disease is a distinctly rare event. Finally there are no uniform guidelines that have been established for the follow-up of patients who have undergone surgical treatment of RCC.

KEY WORDS: Renal cell carcinoma, RCC, partial nephrectomy, Radical nephrectomy.

INTRODUCTION

Renal cell carcinoma (RCC) is the most lethal of the common urologic cancers, and accounts for 90% of renal malignancies in adults⁽¹⁻³⁾. There is a 2 to 3 times predominance of males over $females^{(1,2,4)}$, and the median age at diagnosis is 65 years. However, most patients are in the 6^{th} to 8^{th} decade of life^(2,4). RCC is the most frequently occurring solid lesion within the kidney and comprises different types, and according 2004 WHO Classification of adult renal tumors, the basic categories consist of clear cell, papillary and chromophobe tumors, which account for 70%, 10-15%, and 5%, respectively⁽¹⁾. Bilaterality and multifocality is more common in papillary RCC and accounts 4% and 22.5% respectively while in clear cell RCC accounts less than $< 5\%^{(1,5,6)}$. Factors implicated in the development of RCC include cigarette smoking, exposure to petroleum products, obesity, diuretic use, cadmium exposure, and ionizing radiation⁽⁷⁻¹³⁾.

Most RCCs are discovered incidentally during imaging studies of unrelated clinical indications⁽¹⁴⁻¹⁷⁾. By advancement of imaging techniques, the number of incidentally discovered renal masses increased from 10–15% to over 50% during the last 20 years⁽¹⁸⁻²⁰⁾. Current radiologic techniques cannot distinguish histologic subtype of the small renal cortical neoplasms, however; most of incidentally discovered renal cell carcinomas are small, low stage tumors⁽²¹⁻²³⁾.

Unfortunately, despite the increased incidental detection rate, the mortality from RCC has remained unaffected and parallel to the incidence. The explanations of this phenomenon in part, by the fact that some of small cancers have aggressive behavior⁽²⁴⁻²⁶⁾, as well as the rate of discover of large aggressive cancers still not declined⁽²⁷⁾. The intensity, frequency and duration of follow-up as well as investigations required during this period are varying from center to center⁽²⁸⁻³³⁾.

The aim of study is to evaluate the cases of renal cell carcinoma regarding the age and the sex of patients presented with renal tumor, symptoms at the time of presentation, physical findings, results of laboratory investigations, imaging study results and complications of surgery as well as histopathological results.

MATERIALS AND METHODS

A retrospective study was performed by reviewing 23 patient's files of genuine cases of renal cell carcinoma who admitted to Urology center and Benghazi medical center in the period from August 2009 to August 2014.

RESULTS

The following table and figure shows the age group distribution of the numbers of the cases as follow; 2 cases were below 40 years, 4 cases were between 41 and 50 years, 7 cases were between 51 to 60 years, 5 cases were between 61 and 70 years old and 3 cases were between 71 and 80 years old; however 2 cases were above 80 years old. That represented (8.6%), (17.3%), (30.4%), (21.7%), (13.04%) and (8.6%) respectively. However, the peak incidence of occurring of RCC between 51-60 years of age and represents approximately 52% of all cases. The total number of cases was 23, the youngest patient reported to has RCC was 36 years and the oldest patient was 82 years old (Mean age 59 years) (table 1) and (figure 1).

| (Table | 1) | Age | dist | ributior | ı |
|--------|----|----------|------|----------|---|
| · · | | <u> </u> | | | |

| Age groups | Number | Percentage |
|--------------------|--------|------------|
| <40 years | 2 | 8.6% |
| 41-50 years | 4 | 17.3% |
| 51-60 years | 7 | 30.4% |
| 61-70 years | 5 | 21.7% |
| 71-80 years | 3 | 13.04% |
| >80 years | 2 | 8.6% |
| Number of patients | | 23 case |



The sex distribution of occurrence renal tumors were as follow, 14 cases were male and 9 case were females of different age groups which represents about (61%) and (39%) respectively. The ratio of male to female is 1.6:1. (Table 2) and (figure 2) shows more details of sex and age groups distribution.

| (Tuble 2) bex and age groups distribution | | | | |
|---|------------|------------|--|--|
| Age groups | Male | Female | | |
| <40 year | 1 (4.3%) | 1 (4.3%) | | |
| 41year50 year | 3 (13.04%) | 1 (4.3%) | | |
| 51 year60 year | 4 (17.3%) | 3 (13.04%) | | |
| 61 year70 year | 3 (13.04%) | 2 (8.6%) | | |
| 71 year80 year | 1 (4.3%) | 2 (8.6%) | | |
| >80 year | 2 (8.6%) | | | |
| Number of patients | 14 | 9 | | |



Ten (43.4%) patients mentioned to be smokers, 12 (52.1%) patients were hypertensive, 15 (65.2%) patients were diabetics, all of these may considered as a risk factor of RCC. However, no other possible risk factors were mentioned in the files of patients like obesity because the weight of patients was not mentioned in files.

The renal cell carcinoma has variable presentations ranged from asymptomatic disease which discovered incidentally to the most aggressive disease may presented with symptoms of advanced diseases (table 3) and (figure 3).

| (Table 3) | Symptoms 1 - | at the time | of presenta | tior |
|-----------|--------------|-------------|-------------|------|
|-----------|--------------|-------------|-------------|------|

| Presentation | Number | Percentage |
|---|--------|------------|
| Incidental | 7 | 30.4% |
| Hematuria | 3 | 13.04% |
| Hematuria & flank pain | 2 | 8.6% |
| Abdominal mass and flank pain | 2 | 8.6% |
| Flank pain | 5 | 21.7% |
| Classical triad | 3 | 13.04% |
| Metastatic symptoms with Hema- turia or flank pain | 1 | 4.3% |
| Number of patients | 23 | Cases |



All patients were examined thoroughly and the physical findings were as follow; no obvious physical findings in 12 (52.1%) cases, palpable abdominal mass in 9 (39.1%) cases, weight loss in 1 (4.3%) case, and bilateral lower extremity edema were detected in 2 (8.6%) cases however cervical LAP and non-reducible varicocele were not detected in any case (table 4).

| Physical findings | No. | % |
|---------------------------------------|-----|-------|
| No obvious physical findings | | 52.1% |
| Palpable abdominal mass | | 39.1% |
| Weight loss | 1 | 4.3% |
| Cervical lymphadenopathy | | |
| Bilateral lower extremity edema | 2 | 8.6% |
| Nonreducing or right-sided varicocele | | |

All patients underwent laboratory investigations and the results were as follow, 10 (43.4%) patients have no abnormal laboratory results, 2 (8.6%) patients have mild renal impairment because of diseased contralateral kidney, 1 (4.7%) case show hepatic impairment due non metastatic liver involvement, hypercalcemia was reported in 1 (4.7%) case, ESR was high in 7 (30.4%) cases, and 8 (34.7%) cases were anemic however polycythemia was detected in 2 (8.6%) cases. Note some investigations not done for all patients like ESR (table 5) and (figure 4).



The imaging studies (CT scan, MRI) were used for detection the side, site, and size of the tumor as well as for evaluation of regional lymph node and vena cava involvement and presence or absence distal metastasis. No trial of percutaneous needle biopsy was performed even for small renal mass which appears like benign lesions in imaging studies.

| Investigation results | Number | Percentage |
|---|--------|------------|
| No abnormal lab results | 10 | 43.4% |
| Renal impairment | 2 | 8.6% |
| Hepatic dysfunction (Stauffer's syndrome) | 1 | 4.3% |
| Hypercalemia | 1 | 4.3% |
| High ESR | 7 | 30.4% |
| Anemia | 8 | 34.7% |
| Polycythemia | 2 | 8.6% |



Out of 23 patients, 10 (43.3%) patients have right renal tumors while left side renal tumors detected in 11 (47.8%) cases; however, bilateral renal tumors detected in 2 (8.6%) cases. That mean there were 25 kidneys were involved in 23 patients (table 6) and (figure 5, 6).

| (Table 6) | Side | of rer | nal tui | nor |
|-----------|------|--------|---------|-----|
|-----------|------|--------|---------|-----|

| Age groups | No. | Right | Left | Bilateral |
|------------------------------------|-----|------------|------------|-----------|
| Less than 40 year | 2 | 1 (4.3%) | 1 (4.3%) | |
| 41year50 year | 4 | 2 (8.6%) | 1 (4.3%) | 1 (4.3%) |
| 51 year60 year | 7 | 4 (17.3%) | 3 (13.04%) | |
| 61 year70 year | 5 | 3 (13.04%) | 1 (4.3%) | 1 (4.3%) |
| 71 year80 year | 3 | | 3 (13.04%) | |
| More than 80 year | 2 | | 2 (8.6%) | |
| Number of patients | 23 | 10(43.4%) | 11(47.8%) | 2(8.6%) |
| Number of affected kid- neys | 25 | 10(40%) | 11(44 %) | 4(16%) |



The following table and figure shows more details regarding the side of the tumor according to the age and sex distribution.

Out of 14 male patient having kidney tumors, 7 (30.4%) patients have right renal tumors, 6 (26.01) patients have left renal tumors, while one male have bilateral renal tumors 1 (4.3%). However out of 9 female patients, there were 3 (13.04%) patients have right renal tumors, 5 (21.7%) patients have left renal tumors, while one female have bilateral renal tumors 1 (4.3%) (table 7) and (figure 7).

| Age | Right | | Left | | Bilateral | |
|--|----------------------|-----------------------|----------------------|----------------------|---------------------|---------------------|
| groups | Male | Female | Male Female | | Male | Female |
| Less than 40 years | 1 | | 1 | | | |
| 4150 years | | 2 | | 1 | | 1 |
| 5160 years | 3 | | 2 | 2 | - | - |
| 6170 years | 2 | 1 | 1 | | 1 | - |
| 7180 years | | | 1 | 2 | | |
| More than80 years | 1 | | 1 | | | |
| Number of patients (23) | 7 ^(30.4%) | 3 ^(13.04%) | 6 ^(26.01) | 5 ^(21.7%) | 1 ^(4.3%) | 1 ^(4.3%) |
| Number of affected kidneys (25) | 7 ^(28%) | 3(12%) | 6 ⁽²⁴⁾ | 5 ^(20%) | 2 ^(8%) | 2 ^(8%) |

(Table 7) Side of renal tumor

The bilateral renal tumor which detected in two patients one of them is synchronous and the other asynchronous. In the patient with asynchronous kidney tumor about 2 years passed before appearance of tumor in contralateral kidney.



(Table 8) shows the imaging studies results regarding the size of the tumor, where (60%) of renal tumors size was less than 7 cm in diameter, while (40%) of tumors size was more than 7 cm in diameter.

Out of 25 recorded renal tumors, there were 15 renal tumors less than 7 cm in diameter distributed as follow, 2 (8%) renal tumors in patients less than 40 years old, 4 (16%) renal tumors in patients between 41 to 50 years age group, 5 (20%) renal tumors in patients between 51 and 60 years age group, and 1 (4%) renal tumor in patients between 61 and 70 years age group, 3(12%) renal tumors in patients between 71 to 80 years age group. However, other 10 renal tumors were more than 7 cm in diameter and distributed as follow, 1 (4%) renal tumors in patients between 41 and 50 years age group, 3 (12%)

renal tumors in patients between 51 and 60 years age group, 4 (16%) renal tumors in patients between 61 to 70 years age group, and 2 (8%) renal tumors in patients more than 80 years age group (table 8) and (figure 8).

| Age groups | Number | < 7 cm | >7 cm | |
|-------------------------------|-----------|----------|----------|--|
| Less than 40 years | 2 | 2 (8%) | | |
| 41 years50 years | 5 | 4 (16%) | 1 (4%) | |
| 51 years60 years | 8 | 5 (20%) | 3 (12%) | |
| 61 years70 years | 5 | 1 (4%) | 4 (16%) | |
| 71 years80 years | 3 | 3 (12%) | | |
| More than 80 years | 2 | | 2 (8%) | |
| Number of affected kidneys | 25 Tumors | 15 (60%) | 10 (40%) | |





(Table 9) and (figure 9) show the age distribution renal tumor sites, the sites of renal tumor were 14 (56%) tumors at upper pole, 1 (4%) at mid portion, 7 (28%) at the lower pole and 3 (12%) tumors were diffuse.

| (Table 9 |) Site | of renal | tumor |
|----------|--------|----------|-------|
|----------|--------|----------|-------|

| Age groups | Patients | Kidneys | Upper Pole | Mid Portion | Lower pole | Diffuse |
|-----------------------|----------|---------|---------------|----------------|---------------|------------|
| Less than 40 years | 2 | 2 | | | 2 | |
| 41years-50 years | 4 | 5 | 2 | | 1 | 2 |
| 51 years-60 years | 7 | 7 | 4 | | 2 | 1 |
| 61 years-70 years | 5 | 6 | 4 | 1 | 1 | |
| 71 years-80 years | 3 | 3 | 2 | | 1 | |
| More than 80 years | 2 | 2 | 2 | | | |
| Number of patients | 23 | 25 | 14 (56%) | 1 (4%) | 7 (28%) | 3 (12%) |



The perinephric fat was involved in 5 (21.7%) patients, renal vein or IVC were involved in 5 (21.7%) patients, 1 (4.3%) cases had pulmonary metastasis, and 4 (17.3%) had regional lymph nodes by cross sectional images.

Therapeutic radical nephrectomy was done for 13 (56.5%) cases while partial nephrectomy was done for 3 (13.04%) cases because their contralateral kidneys were diseased and primary tumor is small either in upper pole or lower pole of kidney. Two of patients underwent partial nephrectomy; already have mild impairment of renal function which is minimally deteriorated after surgery. However, palliative radical nephrectomy was done in 4 (17.3%) cases present with advanced renal cell carcinoma. Two (8.6%) young patients presented with bilateral renal tumor sent to special center for performing nephron-sparing nephrectomy, one of them have synchronous bilateral renal mass discovered incidentally during ultrasonic examination of left renal colic, while the other has history of right nephrectomy as a treatment of renal cell carcinoma 2 year before discovering of renal mass in contralateral kidney. One (4.3%) old patient has non-operable locally advanced disease with distal metastasis received only supportive therapy.

So out of 23 cases only 20 (86.9%) patients were operated. The operative findings of 20 cases underwent surgery were as follow; tumor confined to Gerota's fascia in 14 (70%) cases without obvious evidence of lymph node involvement, and the tumor invades Gerota's fascia with thrombus formation in renal vein with scattered lymph node enlargement in 2 (10%) cases, while in the 4 (20%) cases who underwent palliative radical nephrectomy the Gerota's fascia was grossly invaded, the renal vein infiltrated with formation of thrombus in vena cava and the regional lymph nodes were grossly involved. Seven (50%) of 14 cases in whom upper pole was involved the ipsilateral adrenal gland was removed because of imaging or intra-operative suspicious infiltration of Gerota's fascia.

No obvious complication were recorded apart from intra-operative bleeding during resection of the renal mass and removal of vena cava thrombus or during performing partial nephrectomy that can be controlled during surgery, however preoperative and postoperative blood transfusion required in 9(45%) cases.

The histopathological results of resected renal masses as follow conventional (clear-cell) cell carcinoma in 10 (50%) cases, papillary-cell carcinoma in 3 (15%) cases Chromophobe-cell carcinoma 1 (5%), however, Unclassified-cell carcinoma in 6 (30%) cases.

During follow up some patients were missed after a period 6 months to 3 years of follow up and some patients who were diagnosed and operated in 2014, the period of follow up does not exceeds 3 months when the study was prepared, however about 60% of patients followed up without any evidence of recurrence and in most of them the tumors were small and confined within Gerota's fascia.

DISCUSSION

Incidentally discovered renal tumors are confined within the renal capsule in 75% of cases and are associated with a 5-yr survival rate of at least 75% following operative treatment⁽³⁴⁻³⁶⁾, that encourages the more liberal application of partial nephrectomy for smaller renal carcinomas (nephron-sparing surgery)⁽³⁷). Currently, about 90% of such renal masses are RCCs or renal oncocytoma; the remaining masses are benign complex cysts or unusual tumors such as sarcoma or metastases⁽³⁸⁾. Generally, preoperative percutaneous needle biopsy or aspiration of the clinically localized solid renal mass is not recommended because of the high rate of RCC or oncocytoma in such masses, because of high rate of false-negative results, and the possibility of causing bleeding or tumor-tract seeding⁽³⁹). So, percutaneous needle biopsy is reserved only for patients having metastatic lesions to confirm the diagnosis of metastatic RCC and to initiate systemic treatment as well as to get access to a clinical trial⁽⁴⁰⁾. RCC is associated with microscopic and gross hematuria, anemia, weight loss, malaise, acute varicocele, and fever as well as symptoms and signs of polycythemia and hypercalcemia⁽⁴¹⁾. About 30% of RCC cases present with metastatic or locally advanced disease⁽⁴²⁾ so chest xray and abdominal and chest CT scan are strongly recommended to detect early metastatic changes in these areas because they are the most common sites of early metastatic disease^(43,44). Doppler ultrasound or MRI is performed to confirm the CT scan findings when there is suspicion of renal vein and or inferior venacaval involvement as well as to define the extent of thrombus⁽⁴⁵⁾.

Surgical resection still remains the only effective treatment for clinically localized renal tumors. Mortensen (1948) reported the first radical nephrectomy; an operation that removed all of the contents of Gerota's fascia in an attempt to address the 13% of patients with renal tumors that invaded the perinephric fat⁽⁴⁶⁾. The radical nephrectomy was popularized in the 1960s by Robson, who described this operation as the perifascial resection of the tumor-

bearing kidney, along with perirenal fat, regional lymph nodes, and the ipsilateral adrenal gland⁽⁴⁷⁾. Despite the wide acceptance of radical nephrectomy by urologic surgeons for RCC⁽⁴⁸⁻⁵⁰⁾, no data have convincingly confirmed the need for the component parts of the operation i.e., the need for adrenalectomy⁽⁵¹⁾, or the need for and extent of lymph-node dissection^(52,53). Guiliani and colleagues correlated tumor stage with degree of lymph-node metastases and found that tumors confined to Gerota's fascia had a 13% rate of positive nodes, whereas for tumors beyond Gerota's fascia the rate was 37%⁽⁵⁴⁾. About 24% of patients found to have metastatic involvement one adrenal gland appear abnormal on preoperative imaging⁽⁵⁵⁾.

Partial nephrectomy is performed for bilateral renal tumors (*either synchronous or asynchronous*)⁽⁵⁶⁾, for resection of tumor in a solitary kidney, or when the kidney contralateral to the tumor-containing kidney is functionally impaired. At least 20% of functioning remnant of partially resected kidney is needed to maintain a patient off dialysis^(57,58). Approximately 23% of RCCs will display renal-vein extension, and in 7% there will be direct extension of the thrombus into the vena cava⁽⁵⁹⁾. Although the imaging tools like ultrasound and CT can detect vena-caval thrombus, MRI most effectively determines the uppermost extent of the thrombus and obsoletes the need of vena cavography as a diagnostic $tool^{(60)}$. Historically, local recurrences in the renal bed without metastatic disease were reported in approximately 5% of patients undergoing radical nephrectomy⁽⁶¹⁻⁶³⁾. RCC is resistant to chemotherapy and hormonal therapy, and no agent or combination of agents currently achieves a response in more than 10% of patients⁽⁶⁴⁾.

CONCLUSION

The widespread use of abdominal computed tomography and ultrasonography during the diagnostic imaging of nonspecific abdominal complaints has led to the increased detection of incidental small renal masses causing no obvious symptoms. For these clinically localized renal tumors; surgical resection still remains the only effective treatment. Partial nephrectomy for small renal tumors; especially in patients having renal impairment, and for patients having bilateral RCC provides a surgical challenge that balances complete resection with attempts to maintain adequate renal function off dialysis. Most patients with RCC and vena-caval tumor thrombus are entirely symptomless but patients can present with pulmonary emboli, clinical evidence of peripheral venous hypertension (leg edema, collateral venous distention, right-sided varicocele, or caput medusae), and positional hypotension.

Local recurrence without evidence of metastatic disease is a distinctly rare event in RCC, and is usually a precursor for the development of metastatic disease. In the absence of effective systemic therapy for metastatic disease, overly compulsive follow-up may diagnose asymptomatic metastatic disease earlier, but may not necessarily provide a therapeutic advantage. Finally there are no uniform guidelines have been established for the follow-up of patients who have undergone surgical treatment of RCC.

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