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Original Article

Radical Nephrectomy for Renal Cell Carcinoma in a Tertiary Care Hospital in Islamabad

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ABSTRACT

Objective: to identify the demographic, laboratory, radiological and histological features of RCC patients presenting to a tertiary care hospital in Islamabad.

Study Design: Cross-sectional study.

Place and Duration of Study: Pakistan Atomic Energy Commission General Hospital, Islamabad Pakistan, from Jan 2014 to Aug 2021.

Methodology: All the patients who underwent radical nephrectomy for histologically confirmed RCC at PAEC General Hospital Islamabad were included in the study. Demographic variables, ultrasound features, laboratory measures, histological types and Fuhrman grading were noted.

Results: A total of 65 consecutive patients were included, which included 38(58.5%) males. The mean age of the patients was 52.6±8.6 years. The most common symptom was flank pain (42.2%). The diagnosis was made incidentally in 26 patients. The most common ultrasound feature was capsule involvement (23, 35.3%), and most cases were Fuhrman Grade-II (22, 48.9%). On histology, clear cell carcinoma was the most common RCC (40, 61.5%). Post-operative early RFT deterioration was noted in 32(49.2%) patients. This was significantly associated with greater tumour size, Fuhrman Grade-III/IV, renal vein thrombosis, gerota fascia, and ureteric involvement. There was no mortality in our study during the admission days until discharge.

Conclusion: Renal cell carcinoma was more common among males and at a later stage of life (5th decade). The most common type was clear cell carcinoma. Post-operative early RFT deterioration was noted in 49.2% of patients. It was associated with greater tumour size, Fuhrman Grade III and IV, renal vein thrombosis, gerota fascia, and ureteric involvement.

Keywords: Clear cell carcinoma, Fuhrman grade, Renal cell carcinoma, Renal vein thrombosis.

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for greater than 90% of the tumours arising from the renal epithelium. RCC is further classified into subtypes which account for more than ten histological and molecular types.[1] Clear cell carcinoma is the most common subtype but cases presenting with papillary carcinoma and chromophobe carcinoma occasionally present to the urology/nephrology department. The treatment modalities are not limited to surgical intervention but also include chemotherapy for cases which progress beyond the local invasion.[2] Among all cancers, RCC is the 13th most common, with a mortality rate of approximately 40%.[3]

According to GLOBOCAN, RCC accounts for approximately 2.2% of all cancers reported worldwide in 2018. An estimated 403,000 patients were diagnosed with RCC; 63.03% were males. Hence, the relative risk of men having the disease was approximately 1.7. The worldwide cumulative risk was found to be 0.69% and 0.35% among men and women. According to a report, the greatest incidence was found to be in North America. The mortality reported by this report accounted for 1.8% of the worldwide deaths associated with RCC. Out of the total of 175,000 deaths, 65.1% were males.[4]

Technology improvement and increased use of imaging modalities, the diagnosis of RCC has become relatively common compared to a decade ago. However, now RCC is being diagnosed incidentally compared to years ago when patients presented with full-blown signs and symptoms. For localized disease best treatment option is surgical resection either open or minimally invasive laparoscopic surgery. However, aggressive chemotherapy has been warranted in case of a disease that spreads beyond the renal region. The agents used for chemotherapy include VEGF (Vascular endothelial growth factor) targeted therapy, checkpoint inhibitors and CTLA 4 (common tumour leukocyte antigen 4). In addition, a novel treatment option, cryoablation, demonstrated a high treatment efficacy rate.[5] Regardless of the treatment, the more important is that with time the prevalence of diagnosed cases is yet to increase. Meanwhile, physicians and

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surgeons are likely to encounter more cases of RCC than ever.

A recent study showed a decline in the overall mortality rate related to RCC. This study has reported a yearly reduction of approximately 7%.[6] This can be explained based on early diagnosis of RCC due to improved diagnostic imaging modalities. A decade earlier, RCC used to present with the classical triad (pain, hematuria and fever), and most cases presented these symptoms at an advanced stage. The typical presentation is usually between 55 to 75 years of age. However, this trend is changing due to the increased prevalence of incidental cases.[7]

Currently, minimal evidence is available in Pakistan focusing on RCC and the characteristics of its presentation. Furthermore, the epidemiology of RCC is variable in temporality and geography, along with changes in the risk factors such as age. Considering this, a study is warranted on the cases dealt with in Pakistan.

METHODOLOGY

This cross-sectional study was conducted at Pakistan Atomic Energy Commission General Hospital Islamabad, from January 2014 to August 2021. After approval from the Hospital Ethical Review Board (IERB study protocol code # PGHI-IRB(DME)-RCD-06-006s), data of patients were obtained from hospital medical records.

The sample size was calculated using the WHO sample size calculator, taking a confidence level of 95%, a margin of error of 6.5%, and a reported prevalence of underwent radical or partial nephrectomy 7 %.[8]

Inclusion criteria: Patients of either gender, age ranging from 10 to 77 years, with confirmed histological diagnosis of RCC followed by nephrectomy and discharge on the third post-operative day, were included in the study through non-probability consecutive sampling method.

Exclusion criteria: All patients without histological confirmation of RCC and those who did not undergo nephrectomy after histological confirmation were excluded from the study.

The collected data included demographic (age, gender and marital status) and clinical data, including presenting symptoms and pre-operative and post-operative laboratory findings (haemoglobin levels, platelets count, total leukocyte count, urea and creatinine levels). Among the imaging modalities, CT scan and ultrasound features of RCC were noted, including tumour dimension, anatomical location, late-rality and findings (renal vein thrombosis, gerota fascia involvement, perinephric fat involvement, ureteric involvement, capsule infiltration, concurrent cysts and concurrent stones). Histopathological findings were also noted, and based on these findings, and the RCC was further sub-classified into its types such as clear cell carcinoma, papillary carcinoma etc. Fuhrman grading criteria,[9] were used for the tumour grading based on histopathological findings, as shown in Table-I.

Table-I: Fuhrman Grading[9]

Grade	Characteristics
Grade I	Small and round cancer cell nuclei. Nucleoli are difficult to see even when the cells are examined with a high magnification lens.
Grade II	Slightly larger and irregularly shaped cancer cell nuclei. Nucleoli are easier to see but only after the cells are examined with a high magnification lens.
Grade III	Obviously irregular and enlarged cancer cell nuclei. Nucleoli are very easy to see even when the cells are examined with a low magnification lens.
Grade IV	Bizarre, extremely irregular and often multilobed cancer cell nuclei. Sarcomatoid and rhabdoid cells are included in this category.

All patients with either one of the urea or creatinine beyond their normal upper limit were regarded as having post-nephrectomy RFT deterioration. Therefore, the cut-off limit was 20mg/dl and 1.3mg/dl for urea and creatinine, respectively.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. The categorical variables such as gender, histological type, ultrasound features, anatomical location, laterality and Fuhrman grading were presented as frequency and percentages. Mean±SD were computed for numeric variables like age, tumour dimension and laboratory measures. Different parameters were compared by using chi-square and independent sample t-test. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of 65 consecutive patients were included in this study, including 38 males (58.5%). The mean age of patients was 52.6±8.6 years. The maximum age was 77 years, and the minimum was 10 years. 39 (60.0%) patients were symptomatic, while 26(40.0%) were diagnosed incidentally. The presenting complaints of patients were flank pain (42.2%), hematuria (37.7%), palpable mass (44.4%), unexplained weight loss (8.8%), lower urinary tract symptoms (13.3%), fever (15.6%), epigastric pain (11.1%), reduced appetite

(6.7%) and vomiting (2.2%). The most common histological type was clear cell RCC, commonly involving the left kidney and upper pole, as shown in Table-II.

Table-II: Histological Types of Tumours Resected, Laterality, Anatomical Location, Ultrasound Features, Tumour Dimensions, Fuhrman Grading and Mortality from Admission to Discharge (n=65)

Histological Type	Frequency(%)
Clear Cell RCC	40 (61.5)
Papillary RCC	13 (20.1)
Chromophobe RCC	6 (9.2)
Renal Medullary Carcinoma	2 (3.1)
Collecting Duct Carcinoma	3 (4.6)
Cystic Oncocytoma	1 (1.5)
Side	
Left	32 (49.2)
Right	31 (47.7)
Bilateral	2 (3.1)
Anatomical Location	
Upper Pole	26 (40.0)
Middle Pole	17 (26.2)
Lower Pole	22 (33.8)
Ultrasound Features	
Renal Vein Thrombosis	6 (9.2)
Gerota Fascia Involvement	12 (18.5)
Perinephric Fat Involvement	16 (24.6)
Ureteric Involvement	9 (13.8)
Capsule Infiltration	23 (35.3)
Concurrent Cysts	10 (15.3)
Concurrent Stones	5 (7.6)
Tumor Dimensions	
Length (cm) (Mean±Standard Deviation)	6.8±2.7
Breadth (cm) (Mean±Standard Deviation)	5.2±2.3
Fuhrman Grading	(n=45)
Grade I	10 (22.2)
Grade II	22 (48.9)
Grade III	7 (15.5)
Grade IV	6 (13.4)
Mortality during Admission to Discharge	
Yes	0 (0.00)
No	65 (100.0)

The comparison between pre-operative and post-operative laboratory measures were shown in the Table-III. In the patients who showed RFTs deterioration, there was a significant difference with their symptoms, histological type, renal vein thrombosis, gerota fascia involvement, ureteric involvement, tumour size and Fuhrman grading, as shown in Table-IV.

DISCUSSION

RCC imparts an oncological burden greater than in previous decades due to improved imaging modalities resulting in increased incidental diagnosis. According to the literature, the 5-years survival rate of RCC is 76%. However, it is still regarded as the deadliest urological cancer worldwide.[9] Survival rate largely depends on the stage of the tumour at the time of diagnosis. Early diagnosis followed by early treatment results in a better prognosis, but as the Fuhrman Grades progress to III and IV, the survivability of the patient reduces considerably. In the case of stage IV metastatic disease, only 12% of patients are likely to survive.[10]

Table III: Comparison between Pre-Operative and Post-Operative Laboratory Measures (n=65)

Laboratory Measures	Preoperative (Mean±SD)	Postoperative (Mean±SD)	*p*-value
Hemoglobin (g/dl)	12.71±1.42	12.67±2.03	0.945
Total Leukocyte Count (cells × 10^9/liter)	7606±1851	9494.00±2783	0.055
Platelet Count (×10^9/L)	270,000±105,000	297,000±137,000	0.624
Creatinine (mg/dL)	0.92±0.31	1.27±0.38	0.010
Urea (mg/dL)	24.00±6.00	36.00±9.00	0.010

The current study gave an epidemiological trend of all patients diagnosed with RCC at our setup and who underwent radical nephrectomy. Our study reports that the disease is more common among males (58.5%) and in the fifth decade of life (mean=52.6 years). This was comparable to a study by Kawaljit *et al*. in 2018, who reported the disease as most common in the 50-59 age group, followed by 60-69 years. In their study, predominantly affected patients were males, with a much greater percentage of 71.5%. However, the study reported a less prevalence of cases found incidentally (11.1%) compared to our figure of 40%. In addition, on histopathology, the majority of the cases were of clear cell carcinoma (75.7%), comparable to our study, where 61.5% of cases were of the same diagnosis.[11] This study did not detail the changes in post-operative laboratory measures and radiological features.

Studies in the subcontinent have reported incidental diagnosis of RCC previously. They have reported percentages up to 25% to 40%.[12,13,14] However, in developed countries where imaging modality is frequently performed, incidental RCC burden is more and is up to 50% of cases.[15] While our study reported 40% incidental cases close to those presented in western literature. Incidental cases are uncommon in developing countries partly because of the low availability of imaging modalities and late presentation to hospitals with severe symptoms of a particular disease.

Table-IV: Comparison of Patients with and without RFT deterioration (n=65)

	RFT Deterioration (n=32)	No RFT Deterioration (n=33)	*p*-value
Age (years)	53.2±9.6	51.7±7.2	0.634
Histological Type			
Clear Cell RCC	16 (50.0%)	24 (72.7%)	0.024
Papillary RCC	6 (18.8%)	7 (21.2%)	
Chromophobe RCC	4 (12.5%)	2 (6.1%)	
Renal Medullary Carcinoma	2(6.3%)	0(0.0%)	
Collecting Duct Carcinoma	3(9.8%)	0(0.0%)	
Cystic Oncocytoma	1(3.1%)	0(0.0%)	
Symptomatic			
Yes	25(78.1%)	14(42.4%)	0.002
No	7(21.8%)	19(57.6%)	
Side			
Left	16(50.0%)	16(48.4%)	0.812
Right	16(50.0%)	15(45.5%)	
Bilateral	2(9.1%), 1 on each side		
Anatomical Location			
Upper Pole	15(46.9%)	11(34.8%)	0.081
Middle Pole	7(21.9%)	10(30.4%)	
Lower Pole	10(31.8%)	12(34.7%)	
Ultrasound Features			
Renal Vein Thrombosis	6(18.8%)	0(0.0%)	0.016
Gerota Fascia Involvement	10(31.3%)	2(6.1%)	<0.001
Perinephric Fat Involvement	9(27.2%)	7 (21.2%)	0.133
Ureteric Involvement	9(28.1%)	0(0.0%)	<0.001
Capsule Infiltration	10(31.3%)	13(39.4%)	0.672
Concurrent Cysts	4(12.5%)	6(18.2%)	0.271
Concurrent Stones	4(12.5%)	1(3.0%)	
Tumor Dimensions			
Length (cm)	7.4±3.5	5.1±2.2	<0.001
Breadth (cm)	6.4±3.1	4.3±1.6	<0.001
Fuhrman Grading			
Grade I	6(18.2%)	8(24.2%)	0.003
Grade II	10(36.4%)	20(60.6%)	
Grade III	8(22.7%)	3(9.1%)	
Grade IV	8(22.7%)	2(6.1%)	
Mortality from Admission to Discharge			
No	32(100.0%)	33(100.0%)	0.174
Yes	0(0.00%)	0(0.00%)	

Previous studies have shown a decline in RFTs of patients after radical nephrectomy. For example, a study conducted in Karachi reported that post-operatively the creatinine levels were found to be 1.29±0.46 mg/dl, which was more compared to the pre-operative value of 1.01±0.24 mg/dl. According to this study, there was a decrease in creatinine by 9.08 ml/min/1.73 m^2. This was observed in 33% of patients.[16] Similarly, another study comparing renal functions in patients who underwent radical, simple, and donor nephrectomy reported that the radical nephrectomy group had approximately 35.6% of patients with post-procedure deteriorated renal function tests.[17] This was comparable to our study, which reported that 49.2% of patients had deteriorated RFT with deranged post-operative values compared to pre-operative ones (Creatinine: 0.92±0.31 vs 1.27±0.38, p=0.010 and Urea= 24±6 vs 36±9, p=0.010).

Focusing on tumour size, the dimensions reported in our study were a length of 6.8±2.7cm and a breadth of 5.2±2.3cm. Other studies have reported sizes of up to 5.22±2.15cm.[18] Another study reported that the size of benign (4.0cm) and malignant tumours (5.4cm) was comparable to ours. The study also reported that malignant tumours were likely to be of greater size.[19]

Considering the radiological features, RCC was concurrently present with IVC involvement in 9.2% of patients, comparable to another study that reported involvement in 10.4% of the cases.[10] International studies report that perinephric involvement is rare and up to 5%.[20] However, our study reported it up to 24.6%. This may be due to the late presentation of the disease in Pakistan. This could also explain the greater tumour size recorded in our study compared to international studies. Regarding capsular invasion, a meta-analysis conducted in China reported that capsular invasion was present in 21.97% of cases which is comparable to our study, which presented a percentage of 35.3%. The study also reported that the greater the invasion of the surrounding structure, the greater the tumour Fuhrman Grade.[21] Similarly, our study reported ureteric involvement (13.8%), concurrent stones (15.3%) and cysts (5.6%) as well, which is reported at similar lower percentages in international studies.[22]

Our study also compared the patients who had RFTs deterioration with those whose RFTs remained normal post-nephrectomy, and results revealed that the greater the Fuhrman Grade, the more will be chances of RFT deterioration (p=0.003). Similarly, the greater the extent of ultrasound involvement, the greater the tumour size. Patients with RFTs deterioration are more likely to be symptomatic (p=0.002). This can be explained by late presentation as progressive tumours are more likely to cause RFT deterioration than the relatively small ones and have a Fuhrman Grade-I/II. This finding was similar to another study which reported that patients with RFT deterioration had a greater tumour size (4.00cm vs 2.90cm, p=0.035) and were high complexity (26.67% vs 11.11%, p=0.0230).[23]

Our study did not demonstrate any mortality as mortality from admission to discharge was noted in our study. However, studies have shown mortality rates ranging from 2.8%(30 days) to 5.8%(90 days).[24] This is comparative to our study because international studies have reported a very small number of deaths up to 30 days after surgery.

In conclusion, the current study added substantiated evidence to current knowledge about RCC. Although multiple studies have been conducted on this topic, consolidated findings with multiple aspects covered in a single patient pool are relatively few. The current study simultaneously outlines symptoms, laboratory measures, ultrasound findings and histological aspects. Minimal studies are present in literature which cover all such aspects with this detail. Hence, this makes the current study distinctive in its terms.

CONCLUSION

RCC was more common among males and at a later stage of life (5th decade). The most common type was clear cell carcinoma. Tumour size can be up to 6.8cm in a single dimension. The most common ultrasound feature was capsule infiltration. Post-operative early RFT deterioration was noted in 49.2% of patients. It was associated with greater tumour size, Fuhrman Grade-III and IV, renal vein thrombosis, gerota fascia, and ureteric involvement.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MR: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

BH: Study design, data analysis, critical review, drafting the manuscript, critical review, approval of the final version to be published.

KA: Drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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