

Renal Cell Cancer: Clinicopathological Profile and Survival Outcomes

Abstract

Background: The incidence of renal cell cancer (RCC) is increasing worldwide. However, scant information is available from the Indian subcontinent regarding its clinicopathological characteristics and survival outcomes. We retrospectively analyzed data of patients suffering from RCC at our center over the last one decade (2004–2013) to generate information on these aspects. **Materials and Methods:** Case records of 423 patients treated between 2004 and 2013 were retrospectively analyzed. Baseline characteristics, histopathological information, and survival outcomes were assessed. Overall survival was calculated from the time of diagnosis to death due to any cause. **Results:** The median age was 52 years (range: 18–87 years). Male: female ratio was 3.5:1. The median duration of symptoms was 3 months (range: 0–24 months). Thirty-five patients (8.3%) were detected in asymptomatic state. The most common symptom was hematuria (53.2%) followed by flank pain (46.3%). The most common histology was clear cell subtype (71.4%). Two hundred and ninety-three (69.3%) patients presented with nonmetastatic disease whereas 130 (30.7%) had upfront metastatic disease. Five-year survival in Stages 1, 2, 3, and 4 was 92.7%, 72.9%, 54.6%, and 11.5%, respectively. **Conclusion:** Younger age, higher male–female ratio, lower proportion of asymptomatic patients, higher proportion of advanced stage at diagnosis, and lower stage-wise survival were some of the key findings.

Keywords: Clear cell, hematuria, renal cell cancer

Introduction

Renal cell cancer (RCC) is an uncommon malignancy. It constitutes <3% of all cancers.^[1] Nonetheless, incidence is currently increasing at a rate of 2% per year in many developed countries.^[2,3] Its frequency is also expected to rise in India due to increasing life expectancy, rising awareness, better diagnostic facilities, and growing prevalence of risk factors such as obesity.^[4] However, there is a paucity of data for RCC from the Indian subcontinent.^[5,6] Hence, to generate more information on Indian cohort of RCC, we retrospectively analyzed data of 423 consecutive patients treated over 10 years.

Materials and Methods

We collected data of patients registered with histopathological diagnosis of RCC from January 2004 to December 2013 from hospital case records. Clinical and laboratory parameters were entered in the predesigned pro forma. Clinical parameters assessed included age, sex, place of residence, family history, occupation,

history of smoking, comorbidities, presenting complaints and duration of illness, stage at the time of diagnosis, duration of follow-up, and time of death. Histopathological parameters included subtypes of RCC, Fuhrman grading, and tumor and lymph nodal staging. Follow-up details were gathered from the date of last outpatient visit, telephonic inquiry, or with the help of a reply postcard. The primary end point was overall survival (OS), calculated from the time of diagnosis to death due to any cause.

Statistical analysis

Descriptive statistics were used to describe demographic and clinical characteristics. Kaplan–Meier method was used to estimate OS. All analyses were performed using SPSS version 20 statistical software (SPSS Inc., Chicago, Illinois, USA). Data were censored on December 31, 2014, or on the date of last follow-up.

Results

Overall, 477 patients were registered with the diagnosis of RCC at our center between January 2004 and December

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2013. Fifty-four individuals were excluded due to lack of sufficient information regarding baseline parameters. Out of the 423 patients included in the analysis, data regarding OS were available for 331 (78.3%) patients. Table 1 lists various baseline characteristics and associated comorbidities. Maximum patients belonged to the age group of 51–60 years [Figure 1]. Twenty-four (4.7%) and 85 (20.1%) patients were <30 and 40 years of age, respectively.

There were no patients with hereditary syndromes implicated in RCC. Most common comorbidities detected were hypertension and type 2 diabetes mellitus [Table 1]. Three patients had chronic kidney disease and two patients each had hepatitis B infection, hepatitis C infection, or renal transplantation.

Clinical presentation

Thirty-five (8.3%) patients had incidental detection of RCC, where abdominal imaging for some other indication led to detection of tumors. The median duration of symptoms was 3 months (range: 0–24 months). Three hundred and eleven (74.1%) patients had symptom duration <6 months and 108 (25.9%) patients had >6 months' duration. The classical triad of hematuria, lump in abdomen, and flank pain was present in 84 (20.2%) patients [Table 1].

Table 1: Baseline characteristics and symptomatology of the patients

Parameters	n (%)
Age (years), median (range)	52 (18-87)
Sex	
Male	330 (78)
Female	93 (22)
History of smoking	181 (42.8)
Comorbidities	
Hypertension	115 (27.2)
Diabetes mellitus	62 (14.9)
Coronary artery disease	23 (5.5)
BPH	28 (8.4)
Hypothyroidism	14 (3.4)
Bronchial asthma/COPD	11 (2.7)
Cerebrovascular disease	8 (1.9)
Others	16 (3.8)
Clinical features	
Hematuria	225 (53.2)
Flank pain	196 (46.3)
Weight loss	139 (32.9)
Lump abdomen	114 (22.5)
Fever	81 (19.5)
Loss of appetite	41 (9.9)
Bone pains	33 (8.0)
Cough	31 (7.7)
Shortness of breath	28 (7.9)
Varicocele	10 (2.4)
Triad of hematuria, lump, and flank pain	84 (20.2)

BPH – Benign prostatic hyperplasia; COPD – Chronic obstructive pulmonary disease

Histopathology

The most common histology was clear cell subtype (71.4%) followed by papillary Type I (9.9%) [Table 2]. Nine patients had pure sarcomatoid histology and one patient had rhabdoid subtype. There were two cases of mucinous spindle cell tumors, one each of tubulocystic and Xp11.2 translocation RCC. Fuhrman grading was available in 90.8% of patients with clear cell or papillary cell histology. Grade 1, Grade 2, Grade 3, and Grade 4 were identified

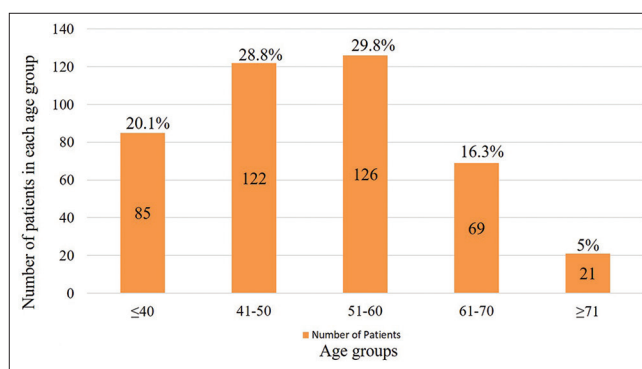


Figure 1: Age distribution of patients

Table 2: Histopathology, pathological tumor stage, and metastatic sites of involvement

	n (%)
Histopathology	
Clear cell	302 (71.4)
Papillary type 1	42 (9.9)
Papillary type 2	25 (5.9)
Chromophobe	4 (3.5)
Oncocytoma	6 (1.4)
Collecting duct	6 (1.4)
Sarcomatoid/rhabdoid	10 (2.4)
Unclassified	14 (3.3)
Others	4 (1)
Tumor stage	
T1a	36 (12.5)
T1b	52 (18)
T2a	49 (17)
T2b	37 (12.8)
T3a	70 (24.2)
T3b	28 (9.7)
T3c	6 (2.1)
T4	12 (4.2)
Site of metastases	
Lungs	77 (59.2)
Bones	68 (51.9)
Distant lymph nodes	41 (31.5)
Liver	33 (25.4)
Soft tissue	21 (16.2)
Adrenals	18 (13.9)
Brain	13 (10)
Skin	7 (5.4)
Other sites	21 (16.2)

in 30 (9%), 140 (41.8%), 110 (32.8%), and 55 (16.4%) patients, respectively.

Stage at presentation

The number of patients in Stages 1, 2, 3, and 4 was 86 (20.3%), 84 (19.9%), 110 (26.7%), and 142 (33%), respectively. Overall, 293 (69.3%) individuals presented with nonmetastatic disease. Table 2 shows tumor stage of patients undergoing curative nephrectomy (289). The most common tumor stage was T3a followed by T1b and T2a. Stage 4 comprised patients with either metastatic (130) or T4 disease (12).

Metastatic sites

Lungs followed by bones were the most common site of distant metastases [Table 2]. Nearly 48% of patients had distant metastases to two or more organ sites whereas 51.5% of patients had single organ site of involvement.

Survival analysis

The median duration of follow-up was 68.7 months (range: 0.5–279 months). Median OS was 79.1 months (range: 0.5–279 months). One-year and 2-year OS were 77.8% and 68.5%, respectively, whereas 5-year OS was 55.1%. Figure 2 shows 5-year survival according to stage at the time of diagnosis.

Discussion

In this analysis, we evaluated the various clinical and histopathological parameters and survival outcomes from a tertiary care center. Median age in our study was 52 years. This is almost a decade lower compared to the median age of 62–64 years reported in studies from Europe and North America.^[2] Other Indian studies have also shown similar age pattern.^[7] Precise mechanisms for this age difference are unclear. The population pyramid in India constitutes of higher proportion of younger population as compared to the West, and this might be one of the reasons for younger age at presentation. Importantly, 24 patients (4.7%) were <30 years of age in our study. There was no feature to suggest a hereditary causation in any of these patients.

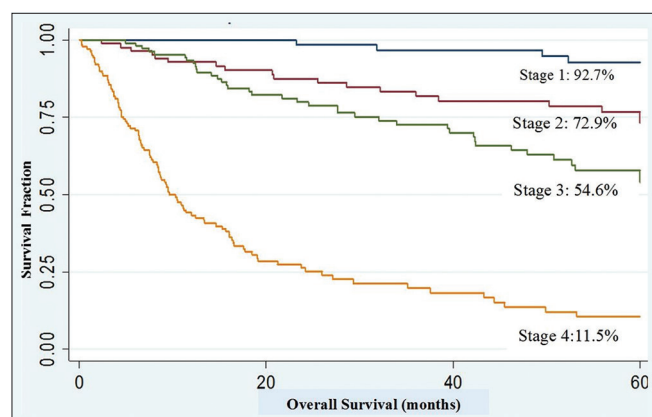


Figure 2: Five-year overall survival according to various stages

RCC in the young should be extensively investigated for genetic causes.

Male-to-female ratio was 3.5:1. Many reports have revealed higher male representation for RCC.^[8] The strongest risk factor for RCC is smoking. In many countries, smoking is more common in males than females and this might account for higher proportion of men for RCC.^[9] In India also, the frequency of smoking in men is much higher than that of women.^[10] Besides, some studies have hypothesized hormonal influences including protective effect of oral contraceptive pills for the lower incidence of RCC in women.^[11,12]

The most common comorbidities detected were hypertension and type 2 diabetes mellitus. Hypertension is one of the established risk factors as well as a paraneoplastic manifestation of RCC.^[13,14] In addition, it has a bearing on the treatment. Anti-angiogenesis therapy, currently the standard of care in metastatic RCC, leads to worsening of hypertension in many patients. This converts into more outpatient visits, higher pill burden by addition of multiple antihypertensive drugs, and increased rate of treatment discontinuation. Patients of diabetes and/or hypertension have propensity to develop chronic kidney disease with radical nephrectomy and hence should undergo functional scans prior to nephrectomy. Partial nephrectomy should be encouraged in such patients.

Two patients had RCC developing in native kidney after renal transplantation. Both these patients were on strong immunosuppressive drugs. RCC of native end-stage kidneys is found in about 4% of patients. End-stage renal disease as well as immunosuppression are risk factors for RCC.^[15-17] The lifetime risk of developing RCC in this group is at least 10 times larger than in the general population.^[16] In addition, these patients have aggressive disease and dismal outcomes.^[17]

Approximately 8.3% of patients were detected in asymptomatic condition. This figure is markedly lower than reports from North America and Europe.^[2,18] In India, thresholds to use abdominal imaging for any indication are higher due to lack of affordability and limited availability. Hence, India is still to see the stage migration of RCC, being seen in the West.^[19] The most common manifestation was hematuria followed by flank pain and weight loss. Interestingly, 20% of patients presented with the conventional triad of hematuria, flank pain, and palpable lump in abdomen. Occurrence of this triad depicts advanced disease. Previous descriptions report its frequency in not >10% of patients.^[20] It reflects greater percentage of patients presenting with advanced disease in our study.

Clear cell carcinoma was the most common histological subtype followed by papillary type I. These findings are similar to that described in literature.^[21] Fuhrman Grade 2 tumors were most common followed by

Grade 3. Importantly, there were 16% of patients with Grade 4 tumors which is higher than reported in other retrospective studies.^[22] Pure sarcomatoid subtype was detected in nine patients. It denotes aggressive disease and is associated with poor survival outcomes.^[23] Two patients had mucinous, tubular, and spindle cell tumor. It is a recently described entity, seen more commonly in females and considered to be a low-grade renal malignancy.^[24] In our study, both patients with this subtype were females with early-stage tumor.

Stage 4 and 3 diseases were more common than Stage 1 and 2 diseases at the time of diagnosis. Majority of studies are currently reporting Stage 1 disease in >50% of patients due to a greater number of asymptomatic detection.^[19] This finding has implications on deciding the line of management and survival outcomes as stage is the most important independent prognostic factor. Furthermore, in our study, higher number of patients presented with thrombus formation. Other than determining stage and prognosis, thrombus removal demands greater surgical expertise and more invasive surgery.

Five-year survival in the study for Stage 1 was equivalent to those reported elsewhere, however 5-year OS for Stages 2, 3, and 4 was lower.^[2,25,26] Five-year OS was 55.1%. This figure is again low compared to many other analyses that have revealed 5-year OS >60%.^[26,27] Few causes can be deciphered for this. First, higher percentage of our patients had Fuhrman Grade 3 and 4 diseases (49.2%) which is an established maker of aggressive disease. Second, in Stage 3, higher number of patients had 3b and 3c Stage due to inferior vena cava (IVC) involvement.^[28] Any kind of IVC involvement adversely affects prognosis.^[29] Third, in the metastatic setting, many patients were not able to afford targeted therapies, lowering survival in Stage 4 disease.

Important limitations in the present study are: first, we did not have follow-up details regarding OS in approximately 22% of patients. Often patients change their contact numbers that do not get updated in the record system and hence could not be traced after stopping outpatient visits. Second, there was missing data regarding body mass index, therefore we could not document the prevalence of obesity in our patients which is a proven risk factor for RCC. Similarly, occupation history was also missing from many case records and consequently no consistent occupational exposure could be found. Last but not the least, this analysis included patients from a single tertiary center, causing potential biases in patient population.

Conclusion

Younger patient population, higher male: female ratio, fewer asymptomatic detection, and higher stage at the time of diagnosis were characteristic features of RCC in this study. Stage-wise survival was inferior in our patients. Though some causes can be deciphered for low survival,

we need to have prospective studies to characterize disease biology and validate risk factors.

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Conflicts of interest

There are no conflicts of interest.

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