Decadal Experience of Renal Cell Carcinoma from a Tertiary Care Teaching Institute in North India

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Abstract

To study the current trends of renal cell carcinoma (RCC) in terms of demographic characteristics, clinical presentation, staging, mode of management, histopathology, and survival characteristics from a high volume tertiary care teaching institute in North India. We retrospectively reviewed the records of all patients of RCC between January 2006 and December 2015 and variables like age, gender, symptoms, tumor size/location/number, stage, type of surgery, histopathology, and survival characteristics were studied. One hundred forty-four patients were included in the study. Most common age group of presentation was 50–59 years (29.8%), male to female ratio was 2.5, and majority of cases were smokers. Flank pain was the most common presenting complaint (38.2%), classical triad (pain, fever, hematuria) was present in 25%, and incidental diagnosis was made in 11.1% cases. Stage T2a was most common presentation with majority of tumors present in upper pole (27.1%). Renal vein involvement (T3a) was present in 10.4%, hilar lymph node involvement in 25%, and distant metastasis was observed in 20.1% cases. Radical nephrectomy was most common surgery performed (75%) and clear cell carcinoma was the most common histopathology (75.7%) followed by papillary (11.1%). Women reported more chromophobe type and low-grade cancers, although rest of clinico-pathological features did not show any gender difference. Mean follow-up of the study was 6–122 months with younger (< 29 years) patients reporting lower 5-year survival and higher stage disease. Renal cell carcinoma shows a different trend in our study population, compared to western data, with large size tumors and advanced stage presentation being more common.

Keywords Renal cell carcinoma · Radical nephrectomy · Partial nephrectomy · Laparoscopic nephrectomy

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of kidney (> 90%) and accounts for 3% of all adult neoplasm. It is the 13th most common malignancy (9th in men and 14th in women) worldwide and most lethal urological cancer with 40% mortality [1]. The typical presentation of RCC is in the 6th and 7th decades of life with racial predominance, associated with poor survival in African Americans [2]. Few decades back, classical triad (pain, fever, hematuria) used to be the most common presentation of RCC, with majority of cases presenting in advanced stage, but with extensive use of ultrasonography (USG) and contrast enhanced computed tomography (CECT), majority of RCC are now incidentally detected

[3]. However, above-mentioned information is derived from western data and Indian statistics are still lacking. Thus, the aim of this study is to examine the trends of RCC in terms of demographic characteristics, clinical presentation, staging, mode of management, histopathology, and survival characteristics from a high volume tertiary care teaching institute in North India.

Subjects and Methods

We retrospectively reviewed the records of all patients presenting with renal mass (clinical/imaging) at our institute between January 2006 and December 2015. Detailed medical records of all the patients were studied and histopathologically (HPE) confirmed renal cell carcinoma (RCC) patients were reviewed. All cases of renal mass reported as benign on histopathology (HPE) were excluded from the study. Variables like age, sex, symptoms, tumor size, location, number, TNM staging, type of surgery (open vs laparoscopic),

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and HPE reports including Fuhrman grade were studied. The seventh edition of American Joint Committee on Cancer TNM staging system was used to classify cancer stage and grade and tumor spread [4]. Histological subtypes were divided as per the classification of World Health Organization [5].

Statistical Analysis

The data of all patients were compared statistically using the chi-square test for categorical variables and Fisher's exact test. *P* value < 0.05 was considered statistically significant. Kaplan Meier's survival curves were applied to calculate the survival of patients based on the age groups and stage of malignancy. We managed all data using SPSS version 16.0 (SPSS, Inc., Chicago, IL) and Graph Pad Prism version 5.0 (Graph Pad Software Inc., San Diego, CA).

Results

One hundred forty-four patients were diagnosed with RCC in the last 10 years at the institute. The most common age group of presentation was 50–59 years [43(29.8%)] followed by 60–69 years [32 (22.2%)] and 40–49 years [29 (20.1%)]. Males constituted majority of cases (71.5%) and majority of patients were smokers (61.1%). Flank pain was the most common complaint at the time of presentation [55 (38.2%)] followed by hematuria in 43 cases (29.9%) and abdominal lump in 22 patients (15.3%). The classical triad (pain, fever, hematuria) was present in 35 cases (24.3%) and incidental diagnosis was made in only 16 patients (11.1%) (Table 1). The majority of tumors were diagnosed in T2a stage (45.5%) followed by T2b and T1b. Majority of tumors were located in upper pole (27.1%) followed by upper mid (26.4%) and lower pole (15.3%). Renal vein involvement was present in 10.4% and IVC thrombus was reported in 04 patients. Twenty-five percent patients had hilar lymph node involvement and distant metastasis was reported in 20.1% cases (liver most common) (Table 2). Radical nephrectomy (open > laparoscopic) was performed in 108 patients (75%) with additional lymph node sampling done in 7.6% cases. Subcostal transperitoneal approach was preferred in majority of patients. Four cases were managed with IVC thrombectomy and three patients with extensive disease underwent cytoreductive nephrectomy. Partial nephrectomy was performed in 6 patients (4.2%) (Table 3). HPE showed clear cell carcinoma as the predominant form (75.7%) [male (68.8%), female (31.1%)], followed by papillary (11.1%) [male (81.25%, female (18.75%)] and other less common types. More than half the patients (54.2%) were Fuhrman's grade 2 followed by grade 3 (30.1%). Grade I was more common in women compared to other grades being more common in men. Pathological stage corresponded with clinical stage in our results with T2a constituting the bulk.

Table 1 Baseline patient characteristics (*n* = 144)

Characteristics	<i>N</i> (%) / mean $\pm$ SD
Age (years)	
< 29	12 (8.3)/23.3 $\pm$ 3.7
30–39	16 (11.1)/34.6 $\pm$ 3.4
40–49	29 (20.1)/43.3 $\pm$ 3.3
50–59	43 (29.8)/53.0 $\pm$ 3.2
60–69	32 (22.2)/62.6 $\pm$ 2.4
> 70	12 (8.3)/72.2 $\pm$ 3.3
Gender	
Male/female	103 (71.5)/41 (27.8)
Smoking	
Smoker/non-smoker	88 (61.1)/56 (38.9)
Hypertension	
Hypertensive/non-hypersensitive	29 (20.1)/115 (79.9)
Co-morbidities	
Diabetes mellitus/hypothyroidism	19 (13.2)
Mean BMI (kg/m ²)	
Men/women	22.4 $\pm$ 4.2/23.6 $\pm$ 4.9
Symptoms	
Incidental	16 (11.1)
Pain	55 (38.2)
Lump	22 (15.3)
Hematuria	43 (29.9)
Pain, lump, and hematuria	35 (24.3)
Hemoglobin (gm%)	
10/> 10	71 (49.3)/73 (50.7); 9.7 $\pm$ 1.8
Total serum calcium (mg%)	8.5 $\pm$ 2.2
Corrected serum calcium (> 10 mg%) (%)	58 (40.27)

BMI body mass index

54.9% cases had organ confined tumor, metastatic disease present in 20.1%, and locally advanced carcinoma in 14.6% patients at presentation. The above-mentioned parameters were more common in men (Table 4). Tyrosine kinase inhibitors (sunitinib/sorafenib) were given in 27 metastatic patients and temsirolimus was given in 2 patients. The mean follow-up of study was 6–122 months. Out of total 144 patients, follow-up records of 25 cases were not available. The 5-year survival was lower in younger age group compared to the older patients and stage I disease patients had better survival than stage IV RCC (Fig. 1a, b).

Discussion

Since the 1970s, the incidence of RCC has increased by an average of 3% per year for whites and 4% per year for blacks [6, 7]. Renal cell carcinoma is the 16th most common cause of cancer death worldwide with highest incidence in

Table 2 Tumor characteristics ($n = 144$)

Characteristics	Number of patients (%)
Size (cm), n (%)	
< 4	04 (2.8)
4–7	35 (24.3)
7–10	67 (45.5)
> 10	38 (26.4)
Laterality, n (%)	
Right	65 (45.1)
Left	73 (50.7)
Bilateral	03 (2.1)
Horseshoe kidney (left/right)	02/01
Tumor location (pole), n (%)	
Upper	39 (27.1)
Mid	12 (8.3)
Lower	22 (15.3)
Upper mid	38 (26.4)
Mid lower	17 (11.8)
All	16 (11.1)
Venous involvement, n (%)	
Renal vein	15 (10.4)
IVC	04 (2.8)
No venous involvement	125 (86.8)
Lymph nodes, n (%)	
Yes/no	36 (25)/108 (75)
Clinical T stage, n (%)	
T1a	04 (2.8)
T1b	35 (24.3)
T2a	67 (45.5)
T2b	12 (8.33)
T3	19 (13.2)
T4	07 (4.86)
Metastasis	
Yes/no	29 (20.1)/115 (79.9)
Metastasis	
Lung	10 (6.9)
Liver	14 (9.7)
Bone	04 (2.7)
Others	01 (0.7)

IVC inferior vena cava

Czech Republic and lowest rates in South East Asia [8, 9]. There is a dearth of demographic and clinico-pathological data from the Indian subcontinent.

About 40% patients with RCC were younger than 50 years in our study similar to that reported by Agnihotri et al. [10]. In our study, 19.4% cases were below 40 years age, 22.2% patients between 60 and 69 years, and 8.3% cases above 70 years. Thus, 69.4% patients with RCC were less than 60 years which is significantly higher than 42% patients below

Table 3 Management and outcomes

Characteristics	Number of patients (%)
Operation	
Operated	133 (92.4)
Non-operated	11 (7.6)
Surgery	
Radical nephrectomy	108 (75)
RN with lymphadenectomy	12 (8.3)
RN with IVC thrombectomy	04 (2.7)
Cytoreductive nephrectomy	03 (2.1)
Partial nephrectomy	06 (4.2)
Type of nephrectomy	
Laparoscopic	10 (6.9)
Open	123 (85.4)
Type of incision	
Anterior subcostal transperitoneal	111 (77.1)
Midline transperitoneal	18 (12.5)
Flank retroperitoneal	15 (10.4)

RN radical nephrectomy, IVC inferior vena cava

60 years reported by SEER database [11], which is one decade lesser than their western counterparts. Similar findings were reported by Sidharth et al. [12]. In our study, gender ratio (male to female) was 2.5:1, marginally higher than gender ratio 2:1 in their western counterparts [13]. This could be attributed to the higher preference to medical facilities and increased consumption of tobacco/smoking by male members in developing countries [14].

Most common mode of presentation in this study was flank pain (38.2%) followed by hematuria alone (29.9%). The classic triad of RCC (pain, intermittent hematuria, and lump) was present in 24.3%, much higher than the western studies (< 10%) [15]. This could be due to the poor economic status and lack of medical services to majority of poor people in developing countries compared to easy availability and screening along with the health insurance in western countries.

Incidental diagnosis was made only in 16 patients (11.1%) of RCC. This is in clear contrast to the previous reported studies from the Indian subcontinent, which reported incidental diagnosis of RCC in 25 to 40% patients [10, 12, 16] and western literature, reporting more than 50% RCC to be detected incidentally [17]. The possible explanation could be that our institution gets referred patients with large tumor burden at later stages and lower literacy rate in patients of poor socio-economic strata, resulting in poor understanding of the gravity and consequences of initial minor complaints leading to delayed presentation.

Majority of patients in this study had 7–10-cm mass followed by more than 10-cm mass. Small renal masses (less than 4 cm) were reported in < 3% cases presenting with small < 4-cm renal mass. Three patients each had bilateral renal

Table 4 Histopathology characteristics ($N = 144$)

Characteristics	Number of patients (%) ($N = 144$)	Male (%) ($N = 103$)	Female (%) ($N = 41$)
Type			
Clear cell	109 (75.7)	75 (68.81)	34 (31.19)
Papillary	16 (11.10)	13 (81.25)	03 (18.75)
Chromophobe	03 (2.10)	01 (33.3)	02 (66.6)
PNET	02 (1.40)	02 (100)	00 (00)
Sarcoma/sarcomatoid changes	02 (1.40)	01 (50)	01 (50)
Others	12 (8.30)	11 (91.67)	01 (8.33)
Fuhrman's grade			
1	13 (9.10)	05 (38.46)	08 (61.54)
2	78 (54.20)	60 (76.92)	18 (23.97)
3	44 (30.10)	32 (72.73)	12 (27.27)
4	09 (6.25)	05 (55.55)	04 (44.44)
Necrosis			
Present	47 (32.60)	30 (63.83)	17 (36.17)
Absent	97 (67.40)	73 (75.26)	24 (24.74)
Pathological T stage			
T1a	04 (2.80)	03 (75)	01 (25)
T1b	35 (24.30)	21 (60)	14 (40)
T2a	67 (45.50)	55 (82.09)	12 (17.09)
T2b	12 (8.33)	08 (66.66)	04 (33.33)
T3	19 (13.20)	11 (57.89)	08 (42.11)
T4	07 (4.86)	05 (71.43)	02 (28.57)
N stage			
0	108 (75)	78 (72.22)	30 (27.77)
1	36 (25)	25 (69.44)	11 (30.55)
M stage			
0	115 (79.90)	83 (72.17)	32 (27.83)
1	29 (20.10)	20 (68.97)	09 (31.03)
Pathological stage grouping			
Stage I (T1N0M0)	16 (11.80)	12 (75)	04 (25)
Stage II (T2N0M0)	60 (43.10)	38 (63.33)	22 (36.66)
Stage III (T1/T2N1M0/T3NanyM0)	43 (31.30)	37 (86.04)	06 (13.95)
Stage IV (T4NanyM0/TanyNanyM1)	25 (18.10)	16 (64)	09 (36)
Tumor spread			
Organ confined (T1-2N0M0)	79 (54.90)	55 (69.62)	24 (30.38)
Locally advanced (T3-4N0M0)	21 (14.60)	13 (61.90)	08 (38.09)
Metastatic (Tany N any M1)	29 (20.10)	20 (68.97)	09 (31.03)
TKI/m TOR			
Sunitinib	10 (6.90)	08 (80)	02 (20)
Sorefinib	17 (11.80)	11 (64.71)	06 (35.29)
Temsirolimus	02 (1.40)	01 (50)	01 (50)

PNET primary neuroectodermal tumor, *TKI* tyrosine kinase inhibitors, *mTOR* mammalian target of rapamycin

tumors (2.1%) and RCC in horse shoe kidney (HSK), similar to previous studies [18]. Most common tumor location was upper pole (27.1%) and upper mid pole (26.4%) with mid pole

being the least common tumor location. Majority of patients were of stage T2a (42.4%) at presentation followed by T2b (17.4%) and T1b (16.7%) respectively. Renal vein and IVC

Fig. 1 **a** Kaplan Meier's survival curve in patients of renal cell malignancy based on different age groups. **b** Kaplan Meier's survival curve in patients of renal cell malignancy based on different stages

involvement was present in 10.4% and 2.8% cases respectively, similar to the previous studies [19]. Crispen et al. [20] reported less than 5% rate of lymph node involvement in RCC compared to 8% in our study.

Twenty percent patients of RCC had distant metastasis at initial presentation and liver (9.7%) and lungs (6.9%) were the most common organs involved. Majority of western studies have reported distant metastasis in 20–30% patients of RCC with majority of deaths occurring due to metastasis in RCC [21].

More than 90% patients underwent surgery and radical nephrectomy (RN) was the most commonly performed in about 70% cases. Lymphadenectomy and IVC thrombectomy were done in additional 8.3% and 2.7% patients respectively. This higher rate of radical nephrectomy in this study is supported by the fact that majority of patients had large tumor size (> 7 cm). Siddharth et al. [12] in their study from Nepal reported radical nephrectomy in 62% cases of RCC.

Clear cell carcinoma (75.7%) was the predominant histopathology form reported in our study followed by papillary (11.1%) and other less common types. Fuhrman grade 2 (54.2%) and grade III (30.1%) were most commonly reported.

Higher chromophobe and lower clear cell and papillary types were reported in women patients. Also females were found to have majority of low grade tumors. Similar findings were reported by Chen J et al. [22]. Previous studies showed the higher incidence of clear cell carcinoma (85%) worldwide [11] and 70–75% in Indian literature [10, 23]. More than half the patients (54.9%) were organ confined at presentation with metastatic disease present in 20.1% and locally advanced renal cell carcinoma present in 14.6% patients at presentation. About 17% patients of RCC worldwide [3] and 30–35% cases in Indian subcontinent had metastatic disease at initial presentation [24].

As already mentioned metastatic disease was present in almost 1/4th patients. All these patients received TKIs including sunitinib, sorafenib, and temsirolimus. Cytoreductive nephrectomy could be performed in only three cases (3/29, 10.34%) cases as majority of these patients had either T4 disease with extensive surrounding organ involvement or were unfit for surgery from anesthesia point of view. Tolerability of TKIs was a major issue as bulk of these patients reported side

effects like gastrointestinal disturbances and hand foot mouth syndrome.

The mean follow-up period in the present study ranged from 6 to 122 months. The 5-year survival was poor in younger (< 29 years) compared to older patients (> 70 years) and 5-year survival decreases with increasing age. Also, early stage disease has better survival. This difference could be explained by the more aggressive nature of RCC in younger patients resulting in higher mortality. Also, aggressive surgical management in early stage cancer might be responsible for better survival. Agnihotri et al. [10] reported better survival in older patients compared to younger cases, which could be attributed to poor nutrition status of patients in developing countries. No difference in the overall survival and disease-specific survival was reported in men and women. Similar findings were reported in previous literature [25–27]. Also, the 5-year survival was lower in higher stage disease similar to the other studies [28].

The strength of this study includes more than 10-year experience of RCC from a tertiary care center in North India, including a high number of patients (144) presenting with large renal masses often in the advanced stages. Our institute is government owned tertiary care center catering to surrounding states and countries, where whole treatment cost of cancer patients is borne by the government. Majority of the patients are poor and illiterate being ignorant of their disease and presenting to the hospital in later stages. Thus, when whole western world is busy concentrating on the minimal invasive (robotic and laparoscopic) nephron sparing approaches for incidentally detected small size RCC, Public sector hospitals in our country still deal with massive size tumors presenting in advanced stages which even makes the open surgery a big challenge. Although, this study represents the data from a single center only and the conclusions made here cannot be generalized to whole country, still the findings give a hint of the current clinico-pathological and demographic trends in RCC especially in rural India.

Conclusion

The demographic and clinic-pathological trends of RCC significantly differ between developed and developing countries. In this era, when developed nations are dealing with robotic surgery, the third world countries still report RCC in advanced stages, younger age groups and massive size renal masses which will make even radical nephrectomy a nightmare. All these factors together impact the 5 year and overall survival of these patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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