

Epidemiological and Histopathological Study of Renal Cell Carcinoma: A Retrospective Study

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ABSTRACT

Introduction: The incidence of Renal Cell Carcinomas (RCCs) has increased steadily and they have become the seventh most common histological type of cancer across the globe.

Aim: To assess the profile of the patients of RCC with respect to age distribution, sex distribution, clinical presentation, site of tumour, risk factors, staging, histopathological examination, and operative complications.

Materials and Methods: A retrospective descriptive study was conducted in Department of Urology, Indira Gandhi Institute of Sciences, Patna, Bihar, India, from January 2019 to June 2020, that included patients of RCC. The pathology specimens and reports of patients with RCC who underwent laparoscopic, open, cytoreductive, and partial nephrectomy were reviewed. Data related to demographic characteristics, site of tumour, risk factors, co-morbidities, clinical features, histopathology, tumour grade and stage, type of surgery, intraoperative and postoperative complications, and Fuhrman nuclear grading system were recorded. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, Illinois, USA).

Results: Total 60 patients diagnosed with RCC were included in this study. Of these, majority of patients were men (n=44). Majority of patients belonged to the age group of ≤60 years (n=39). Smoking (n=30), hypertension (n=30), obesity (n=20), and occupational exposure (n=8) were major risk factors associated with RCC. Haematuria (n=36), flank pain (n=24), haematuria and lump, with flank pain (n=18), and weight loss (n=18) were the most common clinical features in patients with RCC. According to the histopathologic type, 30 (50.0%) patients had clear cell RCC, 18 (30.0%) had papillary RCC, 8 (13.3%) had chromophobe RCC and the other four (6.7%) had cystic neoplasm, urothelial, angiomyolipoma, or sarcomatoid. Twenty-four patients underwent laparoscopic nephrectomy while 31 patients underwent open nephrectomy. Cytoreductive and partial nephrectomy was performed in three and two patients, respectively.

Conclusion: The present study findings suggest that intraoperative and postoperative complications were more common among patients who underwent open nephrectomy.

Keywords: Clear cell carcinoma, Haematuria, Laparoscopic nephrectomy, Smoking

INTRODUCTION

Renal Cell Carcinoma (RCC) is a malignancy originating from the proximal renal tubular epithelium. The RCCs are the seventh most common histological type of cancer across the globe [1]. In India RCC is a serious public health problem and the prevalence is about 2/100,000 in men population and among women it is about 1/100,000 population [2].

There are several risk factors linked to RCC. Smoking is an independent risk factor for developing RCC [3]. Globally, obesity has been estimated to account for over 18% of RCC cases [4]. There is evidence that both obesity and hypertension (HTN) are frequently present in the same patient population. Further HTN is also an independent risk factor for the development of RCC.

The most frequent histological types of RCCs include clear cell RCC, papillary RCC, and chromophobe RCC [1]. Clear cell carcinoma is observed at a frequency of 75% of all RCCs. It mainly arises from the epithelium of the proximal tubule. Papillary RCC accounts for approximately 15% of all RCCs and it mainly arises from the epithelium of the proximal tubule. While chromophobe RCCs have been observed at a frequency of ~5% of kidney tumours. It is thought to arise from the distal nephron and epithelium of the collecting tubule [5,6].

Most of the epidemiological studies of RCC were done in western countries [3,7,8]. Only a few studies from India reported the study on incidence, survival, risk factors, complications, and stages of RCC [9-11]. Such evidence-based studies among the Indian populations were found to be scarce. The present study was conducted to assess the profile of the patients of RCC with respect to age distribution, sex distribution, clinical presentation, site of tumour, risk

factors, staging, histopathological examination, and intraoperative and postoperative complications.

MATERIALS AND METHODS

A retrospective descriptive study was conducted among patients with RCC recruited at Department of Urology, Indira Gandhi Institute of Sciences, Patna, Bihar, India from January 2019 to June 2020. The pathology specimens and reports of patients with RCC who underwent laparoscopic, open, cytoreductive, and partial nephrectomy were reviewed. The study protocol was approved by the Institutional Ethics Committee (EC approval number: 840/IEC/IGIMS/2019).

Inclusion and Exclusion criteria: Patients of either sex, aged 20 years or older, and homogenous renal masses measuring >15 Hounsfield Units (HU) were included. Patients with lipid-rich angiomyolipoma, aged <20 years, enhancement <15 HU, life-threatening co-morbid conditions, and non enhancing renal mass were excluded from the study.

Data Collection

Clinical diagnosis was made by Contrast Enhanced CT (CECT) scans after diagnosis of a renal space occupying lesion. Data related to demographic characteristics (sex, age, and religion), site of tumour, risk factors, co-morbidities, clinical features, histopathology, tumour grade and stage, type of surgery, intraoperative and postoperative complications were collected during routine care. Fuhrman grade, histopathological subtypes, and lymph node involvement were analysed. Fuhrman nuclear grade is the most widely used grading system for RCC. Fuhrman nuclear grading system is a 4-tiered grading system determined by the nucleus shape, size, and nucleolar

prominence [Table/Fig-1] [12]. Staging of RCC was done using the American Joint Committee on Cancer (AJCC) Tumour, Node and Metastases (TNM) system [13]. The TNM staging system are shown in [Table/Fig-2].

Grade	Nuclear shape	Nuclear diameter (in microns)	Type of nuclei
Grade 1	Round and uniform	≈10	Inconspicuous or absent.
Grade 2	Slightly irregular	≈15	Evident
Grade 3	Moderately to markedly irregular	≈20	Large and prominent
Grade 4	Multilobed and bizarre	≥20	Large nucleoli with heavy chromatin clumps.

[Table/Fig-1]: Fuhrman nuclear grading system [12].

Stage	Abbreviation	Stage description
Stage I	T1, N0, M0	The tumour is ≤7 cm located in the kidney. It has not spread to the lymph nodes or distant organs.
Stage II	T2, N0, M0	The tumour is >7 cm located in the kidney. It has not spread to the lymph nodes or distant organs.
Stage III	T3, N0, M0	The tumour is growing into renal vein or the vena cava, or into tissue around the kidney, but it is not growing into the adrenal gland or beyond Gerota's fascia (T3). It may or may not have spread to nearby lymph nodes (N0/N1). There is no spread to the distant organs (M0).
	T1-T3, N1, M0	
Stage IV Metastases	T4, any N, M0	The main tumour is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4). It may or may not have spread to nearby lymph nodes (any N). There is no spread to the distant organs (M0).
	Any T and N, M1	The main tumour may have grown outside the kidney (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant and/or other organs (M1).

[Table/Fig-2]: The TNM staging system.

The primary endpoint was to determine the profile of the patients of RCC in respect to age distribution, sex distribution, clinical presentation, site of tumour, risk factors, staging, histopathological examination, and intraoperative and postoperative complications. In the present study, the postoperative complications were compared between the groups with the Clavien-Dindo classification. The Clavien-Dindo classification is a standardised system for assessing postoperative complications. It was developed by Clavien in 1992 based on the severity of a complication.

- Grade 1: included minor risk events requiring minimal or no intervention.
- Grade 2: complications consists of potentially life-threatening complications requiring therapeutic intervention or a hospital stay.
 - Grade 2a: included complications requiring therapeutic intervention and
 - Grade 2b: included complications requiring an invasive procedure.
- Grade 3: consists of complications leading to lasting disability or organ resection.
- Grade 4: complication indicated death of a patient due to a complication [14].

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were summarised with descriptive statistics, including mean and Standard Deviation (SD) and categorical variables were presented as frequency and percentages. A comparison of quantitative variables between the groups was done using the Chi-square test. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 60 patients visiting the institute were diagnosed with RCC of which 44 patients were men and 16 patients were women. The major attributable risk factors include smoking ($n=30$), obesity ($n=20$), and occupational exposure ($n=8$). The most prevalent co-morbidities in these patients were HTN 30 (50.0%) and benign prostatic hyperplasia 25 (41.7%).

The most common histopathologic type of RCC was clear cell carcinoma (50.0%), followed by papillary (30.0%), chromophobe carcinoma (13.3%), and the other four (6.7%) had cystic neoplasm, urothelial, angiomyolipoma, and sarcomatoid. Twenty four patients (40.0%) underwent laparoscopic nephrectomy while 31 patients (51.7%) underwent open nephrectomy. Cytoreductive and partial nephrectomy was performed in three (5.0%) and two (3.3%) patients, respectively [Table/Fig-3].

Parameters	Number of patients, n (%)
Sex	
Men	44 (73.3)
Women	16 (26.7)
Age (years), mean (SD)	52.0 (15.7)
Age groups (years)	
≤60	39 (65.0)
>60	21 (35.0)
Religion (n=57)	
Hindu	45 (78.9)
Muslim	12 (21.1)
Site of tumour	
Left	34 (56.7)
Right	25 (41.7)
Bilateral	1 (1.6)
Risk factors (n=58)	
Smoking	30 (50.0)
Obesity	20 (33.3)
Occupational exposure	8 (13.3)
Co-morbidities	
HTN	30 (50.0)
BPH	25 (41.7)
DM	21 (35.0)
CVD	17 (28.3)
CAD	6 (10.0)
Hypothyroid	3 (5.0)
Asthma	2 (3.3)
Other	3 (5.0)
Clinical features	
Haematuria	36 (60.0)
Flank pain	24 (40.0)
Haematuria, lump, flank pain	18 (30.0)
Weight loss	18 (30.0)
Lump abdomen	12 (20.0)
Loss of appetite	12 (20.0)
Fever	9 (15.0)
Bone pain	6 (10.0)
Cough	5 (8.3)
Shortness of breathing	5 (8.3)
Varicocele	2 (3.3)
Histopathology	
Clear cell	30 (50.0)
Papillary	18 (30.0)

Chromophobe	8 (13.3)
Other	4 (6.7)
Tumour grading and staging	
T1	18 (30.0)
T1a	6 (10.0)
T1b	12 (20.0)
T2	11 (18.3)
T2a	5 (8.3)
T2b	5 (8.3)
T3a	3 (5.0)
Regional lymph node involvement	
NX	12 (20.0)
N0	45 (75.0)
N1	3 (5.0)
Stage at presentation	
	[n=55]
1	25 (45.5)
2	24 (43.6)
3	6 (10.9)
Type of surgery	
Laparoscopic nephrectomy	24 (40.0)
Open nephrectomy	31 (51.7)
Cytoreductive nephrectomy	3 (5.0)
Partial nephrectomy	2 (3.3)

[Table/Fig-3]: Demographic and histopathological profile (N=60).

Data shown as n (%); BPH: Benign prostatic hyperplasia; CAD: Coronary artery disease; CVD: Chronic vascular disease; DM: Diabetes mellitus; Other histopathology: Cystic neoplasm (n=1); urothelial (n=1); angiomyolipoma (n=1); sarcomatoid (n=1)

Intraoperative haemorrhage (n=5), Gerota's fascia (n=3), pulmonary metastasis (n=2), hepatic metastasis (n=1), unresectable tumour (n=1) was observed in patients who underwent open nephrectomy. Postoperative flank haematoma (n=1), wound infection (n=1), ileus (n=1), pneumonia (n=1), and anaemia (n=1) was observed in patients who underwent laparoscopic nephrectomy [Table/Fig-4]. The association of RCC with age and sex is depicted in [Table/Fig-5].

Parameters	Open nephrectomy (n=31)	Laparoscopic nephrectomy (n=24)
Intraoperative complications		
Haemorrhage	5 (16.1)	1 (4.2)
Gerota's fascia	3 (9.7)	1 (4.2)
Pulmonary metastasis	2 (6.5)	-
Hepatic metastasis	1 (3.2)	-
Unresectable tumour	1 (3.2)	-
Postoperative complications		
Flank haematuria	3 (9.7)	1 (4.2)
Abscess	2 (6.5)	-
Wound infection	1 (3.2)	1 (4.2)
Ileus	1 (3.2)	1 (4.2)
Pneumonia	1 (3.2)	1 (4.2)
Anaemia	1 (3.2)	1 (4.2)
Clavien-Dindo complications		
Grade 1	5 (16.1)	2 (8.3)
Grade 2	2 (6.5)	2(8.3)
Grade 3	2 (6.5)	1 (4.2)
Grade 4 or higher	-	-

[Table/Fig-4]: Intra- and postoperative complications. Data shown as n (%).

DISCUSSION

The present study evaluated the epidemiological and histopathological pattern of RCC and risk factors associated with RCC. The key findings

Parameters	p-value		
	≤40 years (n=16)	>40 years (n=44)	
Age			
Stage; pT1-pT2N0M0	13 (81.25)	25 (56.82)	0.0851
Clear cell carcinomas	10 (62.50)	20 (45.45)	0.2467
Papillary carcinomas	3 (18.75)	15 (34.09)	0.2555
Localized RCC	8 (50.00)	18 (40.90)	0.3025
Gender	Male (n=44)	Female (n=16)	
Stage; pT1-pT2N0M0	31 (70.45)	7 (43.75)	0.0598
Clear cell carcinomas	23 (52.27)	7 (43.75)	0.5627
Papillary carcinomas	14 (31.82)	4 (25.00)	0.6132
Localised RCC	20 (45.45)	6 (37.50)	0.5858

[Table/Fig-5]: Association of RCC with age and sex.

Data shown as n (%); RCC: Renal cell carcinoma. *chi-square test

were; a) majority of the population were men presenting age group of ≤60 years; b) Smoking, obesity, and occupational exposure were common risk factors associated with RCC; c) The most prevalent co-morbidities in these patients were HTN and benign prostatic hyperplasia; d) haematuria, flank pain, lump, and weight loss were the most common clinical features of patients with RCC; e) clear cell carcinoma was the most common histopathologic type of RCC followed by papillary and chromophobe carcinoma; f) intraoperative and postoperative complications were common among patients who underwent open nephrectomy than laparoscopic nephrectomy.

A recent noteworthy study by Qu Y et al., noted that RCC incidence was majorly driven by men than women (69.9% vs. 37.1%) [15]. This finding was in general agreement with previous worldwide and Indian reports showing that the incidence of RCC was more often in men than women [16,17]. The previous study by Abraham G et al., conducted in Northern India reported the prevalence of RCC and it was found to be higher in men than women [2]. Another evidence-based retrospective study reported the higher prevalence of RCC in men than women with a men to women ratio of 2.7:1 [10]. These results were in line with the present study which showed higher incidence of RCC in men, with a men-to-women ratio of 2.8:1. These observations suggest that sex was an independent predictor of the incidence of RCC.

A previous histopathological study from Northern India, revealed that the majority of RCC cases at presentation were between 39 to 59 years of age (~60%) and nearly 40% of patients presented at <60 years of age [11]. Another noteworthy study in Indian literature that had a relatively small sample size (n=142) also showed RCC was predominant in young patients aged <60 years [10]. Similarly, the present study noted the remarkable prevalence of RCC in young individuals aged ≤60 years (65.0%) as compared to older individuals aged >60 years (35.0%). Evidence from a study that included the adult Indian population demonstrated corroborating observations thereby suggesting RCC is relatively frequent among young individuals aged <60 years [18]. Moreover, a decreasing trend in the prevalence of RCC was observed with increasing age groups suggesting an inverse relationship between age and incidence of RCC. In contrast to above-mentioned studies, a recently published population based analysis involving a larger population (n=114,539) noted the higher prevalence of RCC in older patients (58-90 years; 64.9%) as compared to the young adult population (18-57 years; 35.1%) [15].

Several risk factors have been studied. Cigarette smoking, obesity, and Chronic Kidney Disease (CKD) were the major risk factor responsible for increased risk of renal cell carcinoma [19]. Smoking was the most common lifestyle related risk factor seen among this study population. The majority of patients had HTN followed by obesity and occupational exposure. These findings are in concordance with Ray RP et al., wherein smoking, HTN, obesity, and occupational exposure were the factors shown to be strongly associated with RCC [20]. A previous retrospective study by Tsivian M et al., depicted that smoking was consistently associated with advanced RCC. Interestingly, current and former smokers had increased

odds of advanced RCC by 1.5- and 1.6-fold, respectively [21]. The association between obesity and RCC has been documented in many studies [22-24] however the exact mechanism between obesity and RCC is still not understood. Hypertension or its treatment has been linked to the occurrence of RCC [25]. Overall evidence reveals that passive smoking, HTN, obesity, and occupational exposure leads to increased risk for the development of RCC.

In the present study haematuria (60.0%), flank pain (40.0%), and flank pain (30.0%), and weight loss (30.0%) were the most clinical features of RCC. The previous study conducted at Eastern India reported haematuria (53.3%) and flank pain (50.7%) as the most common presenting symptoms in patients with RCC [20]. Another evidence based retrospective study reported haematuria as the most common presenting symptom in 53.1% of patients. While, other less common symptoms reported were pain with haematuria, mass per abdomen, pain with mass, and isolated haematuria [26]. Similar findings were observed in a study done by Datta B et al, which reported flank pain and haematuria in around 73% and 61% of patients, respectively [27]. Therefore, all these evidences along with the present study conclude haematuria and flank pain are the common findings among the patients with RCC.

A recent study by Singh A and Urry RJ, studied the intra- and postoperative complications of laparoscopic and open nephrectomy. Results concluded that blood loss and transfusion rates were significantly lower in the laparoscopy group than in open nephrectomy [28]. A study by Reifsnnyder JE et al., reported that patients who underwent laparoscopy had more major complications (grades 3 through 5) compared to the patients who underwent open nephrectomy [29]. Similar trends were seen in the present study wherein intraoperative and postoperative complications were more common among patients who underwent open nephrectomy than laparoscopic nephrectomy.

Limitation(s)

The major limitations of this study were its single center, single arm study, and small sample size. This considerably limited the result interpretation and indicates a need for well designed prospective studies to validate these results. Further, this study did not record the fatality status of the patients therefore the study could not carry out survival statistics among patients.

CONCLUSION(S)

The present study findings suggest that intraoperative and postoperative complications were more common among patients who underwent open nephrectomy than laparoscopic nephrectomy.

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