RESEARCH ARTICLE

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Patient Reported Weight Loss Predicts Recurrence Rate in Renal Cell Cancer Cases after Nephrectomy

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Abstract

Background: Recurrence of renal cell cancer (RCC) affects approximately one-third of patients after curative nephrectomy. However, studies from the Indian subcontinent have been scarce. We here ddetermine relapse rates and patterns in an Indian cohort. **Methods:** This study included all patients with RCC who underwent nephrectomy from 2004 to 2013 at our centre. Recurrence-free survival (RFS) was calculated from the date of surgery to date of recurrence or death. The Cox regression model was applied to identify significant prognostic factors. **Results:** Overall a total of 292 patients were included. Median age was 50 years (range 19-84 years), with a male:female ratio of 3:1. Radical and partial nephrectomy were performed for 276 (94.5%) and 16 (5.5%) patients, respectively. Clear cell was most common histological subtype (71.2%) and T1, T2, T3 and T4 stages accounted for 89 (30.5%), 86 (29.5%), 105 (36%) and 12 (4.1%) patients, respectively. One hundred and thirty-six patients (46.6%) demonstrated recurrence. Eighty-six (63.2%) relapsed at distant sites, 14 (10.3%) and at locoregional sites whereas 36(26.5%) had both distant and locoregional recurrence. Median time to recurrence was 18 months. Approximately 17.7% of cases had disease reappearance after five years. Factors predicting shorter RFS on multivariate analysis were patient reported weight loss ($p=0.004$), Fuhrman grade 3 or 4 ($p<0.0001$), presence of necrosis ($p<0.0001$) and higher tumour stage ($p=0.005$). **Conclusion:** Compared to previous studies, our patients had higher rates of recurrence in general and locoregional recurrence in particular. However, except for weight loss, other predictive factors remain similar. Finding weight loss as the marker of recurrence emphasises the importance of the simple task of history taking.

Keywords: Renal cell cancer- weight loss- recurrence-free survival- fuhrman grade

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Introduction

Renal cell cancer (RCC) is a malignancy seen in smokers and arises from proximal convoluted tubules. It constitutes less than 3 % of all cancers and is regarded as the most lethal urological malignancy. Currently, a stage shift is being observed due to more and more asymptomatic detection of renal tumors, where the disease is still non-metastatic, and tumor burden is low (Kane et al., 2008). Tumor stage at the time of initial presentation is the single most important factor determining relapse and overall survival (OS) in RCC. Higher the stage, more is the chance of disease relapse after curative nephrectomy (Chevinsky et al., 2015; Frank et al., 2005). Besides stage, other factors predictive of recurrence are the nuclear grade, presence of necrosis, sarcomatoid component, and surgical margin status. In the Indian subcontinent, there is a paucity of data regarding patterns of recurrences and predicting factors. We retrospectively analyzed incidence and recurrence pattern of RCC from our center to improve upon existing information.

Materials and Methods

All patients with tissue diagnosis of RCC who were registered between January 2004 and December 2013 at our centre were included. Clinical, radiological and laboratory parameters were collected & entered in the predesigned proforma. Histopathological parameters included subtypes of RCC, Fuhrman grading, presence of necrosis, any sarcomatoid component, tumour and lymph nodal staging. Tumor stage was classified by American joint cancer committee 2010 classification (Edge et al., 2010). We excluded patients with metachronous RCC in contralateral kidney or incomplete baseline information. Disease recurrence was defined by the reappearance of tumour deposits on one or more imaging- Chest radiograph, CT, MRI, bone scan, 18F-FDG PET-CT with or without histological confirmation. Recurrence-free survival (RFS) was calculated from the date of surgery to the time of recurrence or death. Locoregional recurrence included relapses in renal bed, ipsilateral adrenal gland, and /or retroperitoneal lymph nodes.

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Statistical Analysis

Descriptive statistics were used to describe demographic and clinical characteristics. Kaplan-Meier method was used to construct survival curve. Cox Regression Model (univariate and multivariate) was applied to identify significant prognostic factors. All p values were two-sided, and p <0.05 was considered statistically significant. All Analyses were done using SPSS version 21 statistical software (SPSS Inc., Chicago, Illinois). Data was censored on 31 December 2015 or last follow-up date.

Results

Overall 477 patients were registered with the diagnosis of RCC during January 2004 to December 2013. Out of these, 180 patients were excluded due to incomplete baseline information, missing follow-up details, or presence of upfront metastatic disease. For remaining 297 patients, we included 292 patients who underwent nephrectomy in this analysis. Table 1 shows baseline parameters of the patients. Median age was 50 years (range 19-84 years) and male: female ratio was 3:1.

Surgical Details

Out of the 292 patients, 276 (94.5%) and 16 (5.5%) patients underwent radical or partial nephrectomy respectively. Fifty (17.1%) patients underwent laparoscopic nephrectomy.

Histology

Clear cell RCC was most common histological subtype detected in 208 (71.2%) patients. Papillary type I, papillary type II, chromophobe and other histological subtypes occurred in 30 (10.3%), 16 (5.5%), 14 (4.8%), 21 (7.2%) patients respectively. Sarcomatoid component was detected in 11 (3.8%) cases. In patients with either clear cell or papillary histology with available information on Fuhrman grading (247/254), Fuhrman grade ≤ 2 or >2 was reported in 154 (62.4%) and 93 (37.6%) patients respectively.

Information regarding lymph node status was present in only 97 (33.2%) cases. Out of these, 27 (27.8%) patients had histologically documented lymph nodal involvement.

Tumor Stage

T1 stage was detected in 89 (30.5%) patients; T2 stage was found in 86 (29.5%) patients; T3 was detected in 105 (36%) and T4 was detected in 12 (4.1%) patients (Figure 1). Overall, patients most commonly had T3a disease followed by T1b.

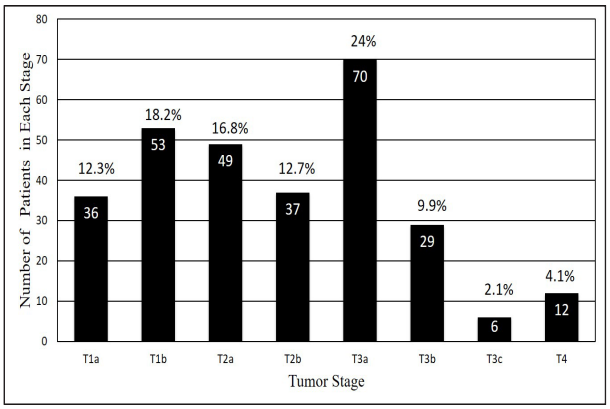

Figure 1. Graph Showing Frequency of Tumor Stages

Table 1. Baseline Characteristics of Patients and Symptoms at Recurrence

Parameter	N (%)
Age in years, median (range)	50 (19-84)
Sex	
Males	221 (75.7%)
Females	71 (24.3%)
Comorbidities	
Hypertension	67 (22.9)
Type 2 diabetes mellitus	37 (12.7)
Symptom duration > 6 months	64 (21.9)
Incidental detection	33 (11.3)
Symptoms at Base line	N/292 (%)
Hematuria	174 (59.6)
Flank pain	140 (47.9)
Weight loss	80 (27.4)
Abdominal mass	55 (18.8)
Fever	48 (16.4)
Triad of hematuria, flank pain, mass	38 (13.2)
Symptom at Recurrence	N/136 (%)
Pain abdomen & /or lump abdomen	22 (16.2)
Bone pains	16 (11.8)
Cough	15 (11.3)
Anorexia	12 (8.8)
Chest pain	7 (5.2)
Neurological symptoms	7 (5.2)
Fever	7 (5.2)
Haemoptysis	5 (3.7)
Shortness of breathe	4 (2.9)
Detected on imaging on follow-up*	14 (10.3)

* Detected on imaging of either abdominal or chest or both

Frequency and Sites of Recurrence

Out of the 292 total patients, 136 (46.6%) patients had recurrence of tumors. Eighty-six patients (63.2%) had distant recurrence, 36 (26.5%) had both distant, and locoregional recurrence whereas 14 (10.3%), had locoregional recurrence alone. The majority of recurrences occurred in first two years (N=77, 56.6%), (Figure 2). Late recurrence i.e. disease appearance after five years occurred in 17.7 % cases (Figure 2). The maximum proportion of patients with T4 (75%) followed by stage 3 (50%) and stage 2 (60.9%) showed recurrence. Only 15 % of stage 1 patients recurred.

Table 2 shows sites of metastases in recurrent setting. Lungs followed by bones were the most common sites of involvement.

Systemic Treatment after Recurrence

Seventy (51.5%) patients received at least one form of systemic treatment. Out of these, 47 (67.1%) patients

Figure 2. Frequency of Recurrence with Time after Initial Diagnosis

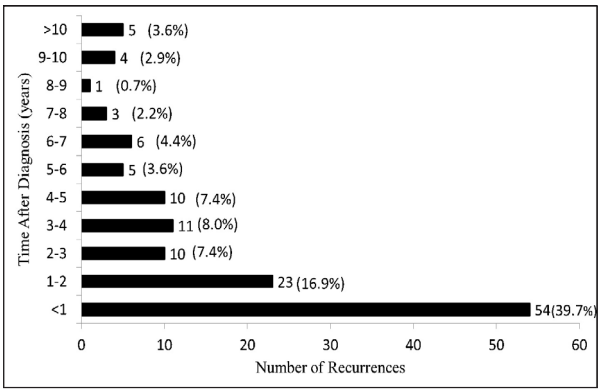

Table 2. Metastatic Sites of Involvement in Patients with Recurrent RCC

Sites	Upon recurrence N (%)
Lungs and mediastinum	64 (52.5)
Bones	54 (44.3)
Liver	35 (28.7)
Distant lymph nodes	22 (18.1)
Soft tissue	14(11.5)
Brain	14(11.5)
Skin	9 (7.4)
Other sites	21 (17.2)

received single line of therapy and 23 (32.9%) patients received two or more lines. Overall, sunitinib, sorafenib, pazopanib, mTOR inhibitors, immunotherapy and other drugs were given to 38 (54.3%), 15 (21.4%), 7 (10%), 19 (27.1%) and 11 (15.7%) patients respectively. None of the patients received bevacizumab-interferon combination.

Factors Affecting RFS

Median follow-up duration was 72.7 months (range 4.8-138 months). Median RFS in stage 1 was not reached, median RFS in stage 2, 3 and 4 were 73.1 months, 37.1 months and 14.9 months respectively (Figure 3).

Table 3 shows factors taken into account to predict recurrence. Univariate analysis revealed- patient reported weight loss, conventional triad of hematuria, flank pain and abdominal mass, Fuhrman grade 3 or 4, presence

Figure 3. Kaplan Meier Graph to Show Recurrence Free Survival in Various Stages

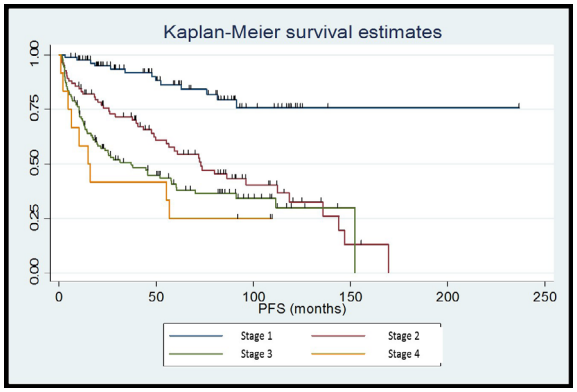

Table 3. Univariate Analysis Showing Factors Affecting Recurrence Free Survival

Parameters	N (%)	HR	95% CI	P value
Age (years)			0 .61 - 1.3	0.539
<60	218 (74.7)	1		
≥ 60	74 (25.3)	1.12		
Sex			0 .75 - 1.72	0.554
Female	71 (24.3)	1		
Male	221 (75.7)	1.13		
Smoking			0.79 - 1.61	0.449
Absent	168 (59.8)	1		
Present	113 (40.2)	1.12		
Hypertension			0.99 - 2.12	0.057
Absent	225 (77.1)	1		
Present	67 (22.9)	1.44		
Duration of symptoms			0 .75- 1.65	0.708
<6 months	224 (77.8)	1		
≥6 month	64 (22.2)	1.12		
Triad*			1.51 -3.49	<0.001
Absent	254 (86.9)	1		
Present	38 (13.1)	2.3		
Weight loss			1.25- 2.52	0.001
Absent	211 (72.5)	1		
Present	80 (27.5)	1.77		
Histology			0.77- 1.66	0.539
Non-clear subtype	84 (28.8)	1		
Clear subtype	208 (71.2)	1.13		
Fuhrman grade			2.28 - 4.78	<0.001
≤2	154 (62.4)	1		
>2	93 (37.6)	3.3		
Sarcomatoid component			2.49- 9.84	<0.001
Absent	281 (96.3)	1		
Present	11 (3.7)	4.94		
Necrosis			1.27- 1.569	<0.001
Absent	181 (64.2)	1		
Present	101 (35.8)	1.41		
Lymph node involvement			1.79- 6.69	<0.001
Absent	56 (67.5)	1		
Present	27 (32.5)	3.46		
Tumors size (cm)				
<10	185 (63.5)	1	1.60- 3.28	0.002
≥10	107 (36.5)	2.29		
Tumor stage				
T1a	36 (12.3)	1	1	
T1b	53 (18.2)	1.24	1.13-1.35	0.341
T2	86 (29.5)	1.94	1.46-2.13	0.082
T3/T4	117 (40)	4.81	3.81-6.69	<0.001

of the sarcomatoid component, presence of necrosis in histology, lymph nodal involvement, tumour size ≥10 cm and T3/T4 tumour stage (all p <0.005) as significant predictors of recurrence.

Factors predicting Shorter RFS in multivariate analysis were patient reported weight loss (hazard ratio

[HR]: 1.83, 95% confidence interval [CI]: 1.22-2.75, p=0.004), Fuhrman grade 3or 4 (HR: 2.56, 95% CI: 1.7-3.86, p<0.0001), Presence of necrosis (HR: 1.3, 95% CI: 1.14-1.48, p<0.0001) and T3/T4 tumor stage (HR: 2.71, 95% CI: 1.53-3.22, p=0.005).

Discussion

This study investigated the pattern of recurrence and prognostic factors in RCC after curative nephrectomy. Approximately 46.6% patients had recurrence of tumor in our analysis. Various studies have reported relapse rates between 15-40 %. (Kobayashi et al., 2003). Importantly, almost 36.8 % patients in our data set had evidence of locoregional disease either alone (26.5%) or in combination with distant metastases (10.3%). A greater proportion of patients presenting with advanced stage might have caused more locoregional and distant metastases in the current analysis. As the stage increases, the chance of distant and locoregional recurrence, worsens. (Frank et al., 2005). In our study, up to 75 % patients with T4 compared to only 15 % patients in Stage 1 disease showed recurrence. Indian studies uniformly show a high proportion of patients with advanced stage of presentation at the time of diagnosis (Agnihotri et al., 2014). On comparison with recurrence pattern in studies from India and west, western reports show lower rates of locoregional recurrences than the Indian studies (Sivaramakrishna et al., 2005; Eggener et al., 2006). Many investigators reporting lower local recurrence rate have included only local tumor site recurrence, unlike the broader definition of locoregional relapse used in the present analysis. It included reappearance not only at renal bed but also retroperitoneal lymph nodes and ipsilateral adrenal glands. Hence our study shows higher locoregional recurrences.

In the current study, 24 patients (17.7%) came with disease reappearance after five years. Various other studies have reported 5-25% incidence of late recurrence in RCC (Park et al., 2012). RCC is known to have late recurrences and hence necessitates life-long follow-up. However, still, we do not have any studies to point out factors predicting late relapses.

Present analysis showed lungs to be the most common site of distant metastases followed by bones-concordant with other reports. Since RCC is known to metastasize to lungs, imaging of chest is part of recommendation during initial work–up and in follow-up. Also, lung metastasectomy is increasingly being performed in RCC, contributing to improved survival rates in the metastatic setting (Zaid et al., 2017).

Approximately 10 % patients had tumor detection on imaging in the absence of symptoms, stressing its importance during the follow-up. Patients while asymptomatic, have good performance status, low tumor burden and in many cases oligometastatic disease, which can be addressed by metastasectomy with curative intent.

Patient reported weight loss, higher Fuhrman nuclear grade, presence of necrosis, and advanced pathological tumor stage were found to be significantly associated with a shorter RFS in multivariate analysis. Although few studies have shown weight loss to be a poor predictor of OS in non-metastatic and metastatic RCC, none of the studies has found it to affect relapse rates. (Bokomeyer et al., 2011; Elson et al., 1988) Ours is the first study where preoperative weight loss has been shown to impact RFS adversely. It emphasizes the need to record the history of weight loss carefully. Many a times patient do not know their body weight before the onset of disease. In these cases, weight loss reporting is based only on subjective observation of themselves and /or family members. This is a potential limitation of this variable. We are yet to find means to measure patient reported variables in objective manner and this remains a felt need. Nuclear grade is an established marker of aggressive disease. In a study by Bretheau et al., nuclear grade correlated with tumor stage, synchronous metastases, lymph node involvement, renal vein involvement, tumor size, and perinephric fat involvement (all $p \leq 0.001$) (Bretheau et al., 1995). Besides, nuclear grade is a valid parameter, predicting the development of distant metastases, as well as locoregional disease after nephrectomy. (Mouracade P et al., 2016; Bretheau et al., 1995). The present study also showed tumor necrosis to predict short RFS. Presence of necrosis in the tumor specimen is a predictor of increased recurrence, shorter disease-free survival, and OS (Ito et al., 2015).

There were some limitations of our study. First was the retrospective nature of assessment. Due to this, our dataset suffers from deficiencies in the record keeping and lack of documentation of various parameters in a standardized manner. Second- lack of information on hilar lymph node involvement, which was available in less than half of the patients. Lymph node positivity is one of the established predictors of recurrence. However, in our study this parameter was not included in the multivariate analysis and hence its impact on RFS could not be evaluated. Third- this analysis included patients from a single tertiary center, causing potential biases in the patient population.

RCC in our cohort manifested with higher stage and consequently higher recurrence rate. Other factors predicting higher recurrence rates were - history of weight loss, high Fuhrman grade and the presence of necrosis. Also, patients continued to show relapses five and ten years after the first diagnosis. We need to have prospective studies to determine factors for late recurrences and decide follow-up duration accordingly. Adherence to follow-up recommendations will help to detect recurrences early when the patient has a therapeutic window and chance of attaining a cure.

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