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A PROSPECTIVE OBSERVATIONAL STUDY ON EFFECTIVENESS OF PROGNOSTIC FACTORS INFLUENCING DISEASE FREE SURVIVAL IN RENAL CELL CARCINOMA

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ABSTRACT: AIMS AND OBJECTIVES: To study the effectiveness of prognostic factors influencing the disease free survival in non-metastatic renal cell carcinoma. To access how well the available study designs such as UNIVERSITY OF CALIFORNIA AND LOS ANGELS and SSIGN could be used to access the prognosis of renal carcinoma on hand. **INCLUSION CRITERIA:** All the patients undergoing radical nephrectomy for renal cell carcinoma above 18 years of age are included in the study. **EXCLUSION CRITERIA:** All the patients with renal cell carcinoma under the age of 18 are excluded. All the metastatic renal cell carcinoma patients were excluded. All the patients with bilateral renal cell carcinoma are excluded. **MATERIALS AND METHODS:** A prospective case series study was conducted after getting approval from thesis committee in the Department of Urology, and followed up in the Department of Urology; Gandhi medical College, Secundrabad, for a period of 12 months from June 2012 to May 2013. **RESULTS:** A total of 30 patients with non-metastatic renal cell carcinoma who underwent radical nephrectomy were followed up for one year. At the end of one year follow up 24 patients (80%) had one year disease free survival. Previous studies to compare prognostic factors of renal cell carcinoma for disease free survival at 1 year are limited and hence the results are compared to studies of five years of follow up. **CONCLUSION:** Our follow-up guidelines after nephrectomy for non-metastatic RCC, based on an integrated stage-specific, and tumor size protocol, stratifying patients in to risk groups showed to be useful to predict recurrence and survival in patients with non-metastatic RCC. Among the clinical related prognostic factors age, mode of presentation had no independent prognostic information at one year of follow up but performance status proved to be a significant prognostic factor. Among tumor related prognostic factors, RCC subtypes and nuclear grade had no independent prognostic value but tumor size, nodal positivity, presence of necrosis and staging had independent prognostic value. Among serum markers, ESR has no prognostic value. The available prognostic models like UCLA and SSIGN designs proved to be useful models for accessing prognosis of non-metastatic renal cell carcinoma at one year of follow up. **KEYWORDS:** Renal cell carcinoma, Radical nephrectomy, Prognostic factors.

INTRODUCTION: Renal cell carcinoma (RCC) is a malignancy with an adverse prognosis for the majority of the patients. Despite an increasing number of patients have incidentally detected RCC, still around 25–30% of patients with new diagnosed disease already have metastatic disease. Of the remaining patients with non-metastatic disease, about 30–40% will progress with distant metastases or local recurrent RCC. Thus, approximately 50–60% of the patients who are clinically diagnosed will die because of progressive disease.⁽¹⁾ Factors predicting the course of the disease are needed to characterize the malignancy in individual patients. Surgery remains the only curative therapy despite the introduction of a number of new promising treatment options.

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Over the last decades new immunotherapies, particularly interferons and interleukins have been evaluated, and have generated promising responses, however, successful in only a minority of the patients.⁽²⁾ Other therapy trials are in progress including stem cell transplantation, gene and vaccine treatment strategies.^(2,3,4,5) Despite new promising therapies, metastatic RCC is one of the therapy resistant malignancies. Therefore, methods to predict which patients are likely to develop (Recurrent) metastases are needed, and it is also important to identify those that respond to various treatments. It is well accepted that RCCs with similar morphology and tumor stage often have a different clinical course.⁽⁶⁾ Identification of good predictors of survival is a basis for future treatment strategies for an individual patient.

One important tool to improve the therapy of RCC, is to use such prognostic factors for identification of patient eligibility for entering into studies and assessing patient response to therapy.^(7,8) Various prognostic models might possibly be superior predicting survival compared with staging and grading. Such staging systems will also include a number of molecular variables characterizing the tumor. This study covers some of the pathological and clinical variables that are today recognized as prognostic factors for RCC.

AIMS AND OBJECTIVES: To study the effectiveness of prognostic factors influencing the disease free survival in non-metastatic renal cell carcinoma. To access how well the available study designs such as UNIVERSITY OF CALIFORNIA AND LOS ANGELS and SSIGN could be used to access the prognosis of renal carcinoma on hand.

INCLUSION CRITERIA: All the patients undergoing radical nephrectomy for renal cell carcinoma above 18 years of age are included in the study.

EXCLUSION CRITERIA: All the patients with renal cell carcinoma under the age of 18 are excluded. All the metastatic renal cell carcinoma patients were excluded. All the patients with bilateral renal cell carcinoma are excluded.

MATERIALS AND METHODS: A prospective case series study was conducted after getting approval from thesis committee in the Department of Urology, and followed up in the Department of Urology, Gandhi hospital, Secundrabad, for a period of 12 months from June 2012 to May 2013. Informed consent is obtained from all the patients. Patients diagnosed to have solid renal mass with enhancement of more than 15 Hounse field units on 128 slice CT scan are categorized as symptomatic and incidental renal tumors on presentation.

The preoperative evaluation consisted of hemogram, renal function tests and metastatic workup with Chest X-ray, Liver function tests and serum calcium. ESR level cutoff was made at 28mm above which was labeled as high below which was labeled as low.

Patients with symptoms or signs of skeletal involvement or elevated alkaline phosphatase underwent bone scintigraphy. Patients with respiratory complaints, abnormal findings on chest x ray and lymphadenopathy on CT abdomen underwent chest CT. Patients with detected metastasis are excluded from the study.

Patients performance status was accessed by Eastern cooperative oncology group performance status preoperatively. All patients underwent radical nephrectomy.

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Radical nephrectomy was routinely performed via a transverse abdominal chevron incision dividing both recti abdominis muscles.

The nephrectomy was performed en bloc, removing the kidney along with perirenal fat and Gerota's fascia. Ipsilateral adrenalectomy was done for upper pole tumors involving adrenal or CT scan evidence of adrenal enlargement. In case of enlarged or palpable lymph nodes between aorta and vena cava, or in other sites, lymph nodes were dissected in that area, but no extensive radical retro peritoneal lymph node dissection was routinely performed. In patients with tumor thrombus in venous system radical nephrectomy was done along with removal of thrombus.

Tumor size was measured as the maximum diameter determined on gross section of specimen. Histopathological nuclear grade was determined, primarily (>80% of pathology reports) by one pathologist following Fuhrman grading system, in line with EAU guidelines and histologically typed by H&E sections if pathology reveals to be renal cell carcinoma. Presence of necrosis and lymph nodal positivity was noted. Tumor stage was defined according to AJCC cancer staging system 2010.

Patients were followed up for 1 year periodically by history, physical examination, blood tests (Renal function tests, serum electrolytes, serum calcium, serum alkaline phosphatase and liver function tests) chest x ray, contrast CT scan abdomen if post-operative renal parameters were normal. Frequency of follow up intervals depends on staging of the tumor.

Following follow up protocols are followed

Pathologic tumor stage	History, examination and blood tests	Chest radiograph	Abdominal CT scan
pT _{1a} N ₀ M ₀	Yearly	---	---
pT _{1b-2b} N ₀ M ₀	Yearly	Yearly	---
pT ₃₋₄ N ₀ M ₀	Every 6 months	Every 6 months for 3 yrs., then yearly	At 1 yr., then every 2 yr.
PTxN ₁ M ₀	Every 6 months for 3 yrs., then yearly	Every 4 months for 2 yrs., then every 6 months	Every 6 months for 1 yr., then yearly
Table 1: Post-operative surveillance after Radical Nephrectomy for localized Renal Cell Carcinoma			

Additional follow-up visits included if patient developed any symptoms with necessary investigations. Recurrence is defined by every new occurrence of renal cell carcinoma after radical nephrectomy local, metastatic recurrence or death from renal cell carcinoma. Disease free survival is calculated from the date of surgery.

After one year of follow up pre and postoperative clinicopathological factors like age, sex, ECOG performance status, ESR levels, mode of presentation, TNM staging, type of histology, Fuhrmans grading, and presence of necrosis are determined and correlated to the disease free survival at one year of follow up. The results are incorporated to prognostic models of renal cell carcinoma like SSIGN and UCLA systems to predict the accuracy of these models in accessing prognosis of renal cell carcinoma.

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RESULTS:

Study design: An observational clinical study

Variables	Disease Free Survival		P value
	No (n=6)	Yes (n=24)	
Age in years			
• <50	3(50%)	10(41.7%)	1.000
• >50	3(50%)	14(58.3%)	
Presentation			
• Incidental	0(0%)	5(20.8%)	0.553
• Symptomatic	6(100%)	19(79.2%)	
T stage			
• T ₁	0(0%)	3(12.5%)	0.025*
• T ₂	1(16.7%)	16(66.7%)	
• T ₃	3(50%)	5(20.8%)	
• T ₄	2(33.3%)	1(4.2%)	
N stage			
• N ₀	4(66.7%)	23(95.8%)	0.094+
• N ₁	2(33.3%)	1(4.2%)	
Nuclear			
• Grade 1	0(0%)	2(8.3%)	0.156
• Grade 2	1(16.7%)	19(79.2%)	
• Grade 3	5(83.3%)	3(12.5%)	
ESR			
• <28	1(16.7%)	13(54.2%)	0.175
• >28	5(83.3%)	11(45.8%)	
Stage			
• Stage 1	0(0%)	3(12.5%)	0.009**
• Stage 2	0(0%)	14(58.3%)	
• Stage 3	3(50%)	5(20.8%)	
• Stage 4	3(50%)	2(8.3%)	
UCLA risk			
• High risk	6(100%)	5(20.8%)	0.001**
• Intermediate	0(0%)	17(70.8%)	
• Low risk	0(0%)	2(8.3%)	
SSIGN score			
• 0	0 (0%)	2 (8.3%)	< 0.001**
• 1-2	0 (0%)	1(4.2%)	
• 3-5	0 (0%)	20(83.3%)	
• 6-8	5(8.3%)	1(4.2%)	

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Variables	Disease Free Survival		P value
	No (n=6)	Yes (n=24)	
• 9-10	1(16.7%)	0 (0%)	
Histology			
• Chromophobe	0(0%)	2(8.3%)	0.158
• Clear cell	3(50%)	19(79.2%)	
• Papillary	2(33.3%)	2(8.3%)	
• Sarcomatoid	1(16.7%)	1(4.2%)	
Necrosis			
• No	0(0%)	22(91.7%)	<0.001**
• Yes	6(100%)	2(8.3%)	
ECOG performance			
• 0	0(0%)	14(58.3%)	<0.001**
• 1	0(0%)	7(29.2%)	
• 2	1(16.7%)	3(12.5%)	
• 3	3(50%)	0(0%)	
• 4	2(33.3%)	0(0%)	
Table 2: Correlation of factors with disease free survival			

One Year Diseases free Survival	No. of Patients	%
No	6	20.0
Yes	24	80.0
Total	30	100.0
Table 3: One year diseases free survival

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DISCUSSION: A total of 30 patients with non-metastatic renal cell carcinoma who underwent radical nephrectomy were followed up for one year. At the end of one year follow up 24 patients (80%) had one year disease free survival. Previous studies to compare prognostic factors of renal cell carcinoma for disease free survival at 1 year are limited and hence the results are compared to studies of five years of follow up.

Majority of patients age was between 40 to 60 years with standard deviation of 53.03 ± 14.9 years (Table 2) This denotes younger age of presentation of renal cell carcinoma in contrast to most common presentation in the sixth and seventh decades of life (Pantuck et al, 2001b; Wallen et al, 2007).⁽⁶⁾ On univariate analysis age was not a significant prognostic predictor for disease free survival at 1 year when the age group of patients were stratified below and above 50 years of age (p value 1) in contrast to Taccon et al demonstrated that young patients, under 40 years old was an independent prognostic factor for the CSS of patients with RCC.⁽⁷⁾ at five years of follow up.

Majority of patient's presentation was symptomatic (83.3%) than incidental (16.7%) (Table 2)

In contrast to more than 50% of RCCs are now detected incidentally (Pantuck et al, 2000).⁽⁶⁾ This denotes delayed presentation of patients to clinician for treatment in our study than reported studies. Incidental tumors had better disease free survival than symptomatic tumors but the mode of presentation was not statistically significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value 0.5) in contrast to studies that incidental tumors are of lower stage and grade, and are less aggressive lesions leading to better patient survival and decreased recurrence. Therefore, the detection of RCC before symptoms enables treatment of less harming tumors and provides a better prognosis for the patient.^(9,10)

Majority of patients had T₂ stage disease and 3 patients had inferior venacaval thrombus below diaphragm with no vein wall invasion (Table 2). 66% T_{3b} patients had no disease free survival at one year. T stage proved to be a moderately statistically significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value 0.025*) as predicted by Several studies demonstrate better survival rates for organconfined disease and document a reduction in survival associated with invasion of the perinephric fat (Kontak and Campbell, 2003; Leibovich et al, 2005a; Lane and Kattan, 2008).^(10,11,12)

Lymph Nodal positivity was noted in 10% of patients (Table 2) and it proved to be a suggested significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value 0.094+) similar to studies showing Lymph node involvement has long been recognized as a dire prognostic sign because it is associated with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively.

Majority of patients had Fuhrmans nuclear grade of 2(66.7%) (Table 2) and no patient had Fuhrmans nuclear grade 4. At 1 year follow up nuclear grade did not prove significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value 0.156) in contrast to Fuhrman grade as significant and independent prognostic parameter for renal cell carcinoma patients in other studies by Lohse CM, Blute ML, Zincke H, WeaverAL and Cheville.^(12,13,14,15)

Majority of patients had clear cell type histology (Table 2) (73.3%). At one year follow up chromophobe type had 100% disease free survival whereas papillary and sarcomatoid types had 50% disease free survival at one year follow up. But type of histology did not prove to be a significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value 0.158). In contrast to studies now suggest that clear cell RCC may have a worse prognosis on average compared with papillary or chromophobe RCC, although there are clearly poorly differentiated tumors in each

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of these subcategories that can be lethal (Moch et al, 2000; Amin et al, 2002; Lau et al, 2002; Cheville et al, 2003; Krejci et al, 2003; Beck et al, 2004).^(16,17,18,19)

Majority of patients had Raised ESR of above 28mm (53.3%) (Table 2) and it did not prove significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value 0.175) whereas elevated erythrocyte sedimentation rate, was independent predictor of cancer-specific mortality in patients with localized clear cell RCC after accounting for other major prognostic factors (Magera et al, 2008).⁽²⁰⁾

Presence of necrosis was noted in (26.7%) (Table 2) of patients and it proved to be a strongly significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value <0.001) similar to the study of Lam et al demonstrated that the presence of histologic TN was an independent predictor of survival in patients with localized disease.⁽²¹⁾ Drawback of this parameter comparison was the amount of necrosis was not made out.

Majority of patients had ECOG performance status of 0(46.7%) (Table 2) it proved to be a strongly significant prognostic predictor of for disease free survival at 1 year on univariate analysis (p value <0.001) similar to finding of the study by Zisman et al, 2001b.⁽²⁰⁾

Majority of patients had tumor stage 2(46.7%) (Table2) and tumor staging proved to be a strongly significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value <0.001) similar to studies where Pathologic stage has proved to be the single most important prognostic factor for RCC (Thrasher and Paulson 1993; Delahunt, 1998; Kontak and Campbell, 2003; Leibovich et al, 2005a; Lane and Kattan, 2008; Kanao et al, 2009).^(21,22,23,24)

Majority of patients had SSIGN score of 3 to 5(66.7%) (Table 2) and SSIGN score proved to be a strongly significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value <0.001) similar to other studies where this system has been validated (Ficarra et al, 2006, 2009; Fujii et al, 2008; Zigeuner et al, 2010).^(24,25,26)

Most of patients had intermediate UCLA risk group (56.7%) (Table2) and this risk stratification proved to be a strongly significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value <0.001) similar to the studies which shows that this risk stratification has been validated internally and externally (Zisman et al, 2002b; Patard et al, 2004c; Cindolo et al, 2006, 2008; Parker et al, 2009).^(27,28,29) The main drawback of the study is small size of the cohort and short follow up period. Multivariate analysis could not be drawn from the study as the sample size was small making such analysis difficult to interpret.

CONCLUSION: Our follow-up guidelines after nephrectomy for non-metastatic RCC, based on an integrated stage-specific, and tumor size protocol, stratifying patients in to risk groups showed to be useful to predict recurrence and survival in patients with non-metastatic RCC. Among the clinical related prognostic factors age, mode of presentation had no independent prognostic information at one year of follow up but performance status proved to be a significant prognostic factor. Among tumor related prognostic factors, RCC subtypes and nuclear grade had no independent prognostic value but tumor size, nodal positivity, presence of necrosis and staging had independent prognostic value. Among serum markers, ESR has no prognostic value.

The available prognostic models like UCLA and SSIGN designs proved to be useful models for accessing prognosis of non-metastatic renal cell carcinoma at one year of follow up.

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