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Original research article

Effectiveness of prognostic factors influencing the disease free survival in non-metastatic renal cell carcinoma

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Abstract

Background: Most individuals with renal cell carcinoma (RCC), a malignancy, have a poor prognosis. Even though an increasing number of people have unintentionally discovered RCC, between 25-30% of those who have just been diagnosed with the disease already have metastatic disease. About 30-40% of the remaining patients with non-metastatic illness will develop local or distant metastases as they proceed. As a result, 50-60% of patients with a clinical diagnosis will pass away from a progressive illness [1].

Objectives

1. To study the effectiveness of prognostic factors influencing the disease free survival in non-metastatic renal cell carcinoma.
2. To assess how well the available prognostic models such as UISS (University of California and Los Angeles Integrated Staging System) and SSIGN score (Stage, Size, Grade & Necrosis) could be used to assess the prognosis of renal cell carcinoma.

Material & Methods

Study design: Hospital based retrospective observational study.

Study area: Sapthagiri Institute of medical sciences and research centre, Bengaluru, Karnataka.

Study period: 1 year.

Study population: All the patients underwent radical nephrectomy for renal cell carcinoma above 18 years of age are included in the study.

Sample size: Study consisted a total of 52 subjects.

Sampling technique: Simple Random sampling.

Study tools and data collection procedure: On presentation, patients who are found to have a solid renal mass on a CT scan with an enhancement of more than 15 Hounse field units are classified as having symptomatic and incidental renal tumors. The haemogram, renal function tests, and metastatic workup including chest X-ray, Liver function tests, and serum calcium were all part of the preoperative evaluation. ESR level cut-off was determined at 28 mm, with high and low levels designated accordingly. Patients who had increased alkaline phosphatase levels or skeletal involvement symptoms received bone scintigraphy. Patients who reported breathing problems, unusual chest x-ray results, and lymphadenopathy on an abdominal CT scan got a chest CT. The study excludes patients with detected metastases.

Results: Majority of patients had SSIGN score of 3 to 5 (67.3%) 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). Most of patients had intermediate UCLA risk group (55.7%) 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).

Conclusion: Our follow-up guidelines after radical nephrectomy, based on an integrated stage-specific, and tumor size protocol, 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.

Keywords: Renal cell carcinoma (RCC), UISS (University of California and Los Angeles integrated staging system) and SSIGN score (Stage, Size, Grade & Necrosis)

Introduction

Most individuals with renal cell carcinoma (RCC), a malignancy, have a poor prognosis. Even though an increasing number of people have unintentionally discovered RCC, between 25-30% of those who have just been diagnosed with the disease already have metastatic disease. About 30-40% of the remaining

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patients with non-metastatic illness will develop local or distant metastases as they proceed. As a result, 50-60% of patients with a clinical diagnosis will pass away from a progressive illness [1].
Characterizing the malignancy in specific patients requires knowledge of factors that can predict the course of the disease. Despite the development of several brand-new, highly promising treatment approaches, surgery is still the only curative therapy available. Recent immunotherapies, particularly interferons and interleukins, have been studied and have produced encouraging results, though they have only been effective in a small proportion of patients [2]. Stem cell transplantation, gene and vaccination therapy trials are now being conducted [2, 3, 4, 5].
Metastatic RCC is one of the cancers that are resistant to treatment, despite new, promising treatments. As a result, it's critical to identify patients who respond to different treatments as well as create methods to forecast which patients are likely to develop (recurrent) metastases. It is widely acknowledged that RCCs with comparable tumor stage and form frequently follow divergent therapeutic paths. The development of effective survival predictors serves as the foundation for developing future treatment plans for a specific patient. Different prognostic models might be more accurate at predicting survival than staging and grading. The goal of this study is to examine some of the pathological and clinical parameters that are currently accepted as RCC prognostic factors.

Objectives
1. To study the effectiveness of prognostic factors influencing the disease free survival in non-metastatic renal cell carcinoma.
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Material & Methods
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Study period: 1 year.

Study population: All the patients underwent radical nephrectomy for renal cell carcinoma above 18 years of age are included in the study.

Sample size: Study consisted a total of 52 subjects.

Sampling technique: Simple Random sampling.

Inclusion criteria: All the patients underwent radical nephrectomy for renal cell carcinoma above 18 years of age are included in the study.

Exclusion criteria
1. All the patients with renal cell carcinoma under the age of 18 are excluded.
2. All the metastatic renal cell carcinoma patients were excluded.
3. All the patients with bilateral renal cell carcinoma are excluded.

Ethical consideration: Institutional Ethical committee permission will be taken prior to the commencement of the study.

Study tools and data collection procedure
On presentation, patients who are found to have a solid renal mass on a CT scan with an enhancement of more than 15 Hounse field units are classified as having symptomatic and incidental renal tumors.
The haemogram, renal function tests, and metastatic workup including chest X-ray, Liver function tests, and serum calcium were all part of the preoperative evaluation. ESR level cut-off was determined at 28 mm, with high and low levels designated accordingly. Patients who had increased alkaline phosphatase levels or skeletal involvement symptoms received bone scintigraphy. Patients who reported breathing problems, unusual chest x-ray results, and lymphadenopathy on an abdominal CT scan got a chest CT. The study excludes patients with detected metastases.
Prior to surgery, the Eastern Cooperative Oncology Group evaluated the patients' performance status. The study included every patient who received a radical nephrectomy. Transverse abdominal chevron incisions were frequently used to accomplish radical nephrectomy. The kidney, perirenal fat, and Gerota's fascia were all removed during an en bloc nephrectomy. For upper pole cancers involving the adrenals or CT scan indications of enlarged adrenals, ipsilateral adrenalectomy was performed. Lymph

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nodes were dissected in the case of swollen or palpable lymph nodes between the aorta and vena cava, or in other places, however comprehensive radical retro peritoneal lymph node dissection was not frequently carried out. Radical nephrectomy was performed in conjunction with thrombus removal in patients who had tumor thrombus in the venous system.

Tumor size was calculated using the specimen's maximal diameter as determined by a gross section. Following the Fuhrman grading method and EAU recommendations, one pathologist largely (>80% of pathology reports) assessed the histopathological nuclear grade and, if renal cell carcinoma was found, histologically classified the tissue using H&E sections. Necrosis and lymph nodal positive were seen. According to the 2010 AJCC cancer staging system, the tumor stage was determined.

For a year, patients were periodically checked on by history taking, physical examination, blood tests (renal function tests, serum electrolytes, serum calcium, serum alkaline phosphatase, and liver function tests), chest x-rays, and contrast CT scans of the abdomen if the patient's post-operative renal parameters were within normal range. The length of follow-up intervals depends on the tumor's stage. Protocols for follow-up are followed.

Table 1: Post-operative surveillance after Radical Nephrectomy for localized Renal Cell Carcinoma

Pathologic tumor stage	History, examination and blood tests	Chest radiograph	Abdominal CT scan
$pT_{1a}N_0M_0$	Yearly	-----	-----
$pT_{1b\text{-}2b}N_0M_0$	Yearly	Yearly	-----
$pT_{3\text{-}4}N_0M_O$	Every 6 months	Every 6 months for 3 yrs, then yearly	At 1 yr, then every 2 yr
$PTxN_1M_0$	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

If the patient experiences any symptoms, additional follow-up appointments with the required tests are covered. Every new instance of renal cell carcinoma following radical nephrectomy is referred to as a recurrence, as is any local, metastatic, or terminal renal cell carcinoma. The date of operation is used to calculate disease-free survival.

Age, sex, ECOG performance status, ESR levels, mode of presentation, TNM staging, type of histology, Fuhrmans grading, and presence of necrosis are pre- and postoperative clinicopathological factors that are determined and correlated to the disease free survival at one year of follow-up. The findings are put into renal cell carcinoma prognostic models like the SSIGN and UCLA systems to determine how well these models predict the prognosis of renal cell carcinoma.

Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Chi-square/ Fisher Exact test have been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

Observations & Results

Table 2: Age distribution of patients

Age in years	No. of patients	%
<30	3	5.7
31-40	3	5.7
41-50	16	30.7
51-60	16	30.7
>60	14	26.9
Total	52	100.0

Mean ± SD: 53.03±14.19.

Majority of patient's age was between 40 to 60 years with standard deviation of 53.03 ± 14.9 years.

Majority of patient's presentation was symptomatic (82.6%) than incidental (17.3%).

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Table 3: T stage distribution of patients

T stage	No. of patients	%
T_1	5	9.6
T_2	28	53.8
T_{3a} T_{3b}	9 5	26.9
T_4	5	9.6
Total	52	100.0

Table 4: N stage distribution of patients

N stage	No. of patients	%
N_O	47	90.3
N_1	5	9.6
Total	52	100.0

Table 5: Nuclear grade distribution of patients

Nuclear	No. of patients	%
Grade 1	4	7.6
Grade 2	34	65.3
Grade 3	14	26.9
Total	52	100.0

Table 6: Type of Histology of patients

Type of Histology	No. of patients	%
Chromophobe	4	7.6
Clear cell	38	73.0
Papillary	7	13.4
Sarcomatoid	3	5.7
Total	52	100.0

Table 7: ECOG performance of patients

ECOG performance	No. of patients	%
0	24	46.1
1	13	25.0
2	7	13.4
3	5	9.6
4	3	5.7
Total	52	100.0

Table 8: SSIGN score of patients

SSIGN score	No. of patients	%
0	3	5.7
1-2	2	3.8
3-5	35	67.3
6-8	10	19.2
9-10	2	3.8
Total	52	100.0

Table 9: UCLA risk group of patients

UCLA risk group	No. of patients	%
High risk	19	36.5
Intermediate	29	55.7
Low risk	4	7.6
Total	52	100.0

Table 10: One year diseases free survival

One year diseases free survival	No. of patients	%
No	9	17.3
Yes	43	82.6
Total	52	100.0

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Table 11: Correlation of factors with disease free survival

Variables	Disease free survival		P value
	No (n=9)	Yes (n=43)	
Age in years			
▪ <50	4(44.4%)	18(41.8%)	1.000
▪ >50	5(55.5%)	25(58.1%)	
Presentation			
▪ Incidental	0(0%)	9(20.9%)	0.553
▪ Symptamatic	9(100%)	34(79.1%)	
T stage			
▪ T_1	0(0%)	5(11.6%)	0.025*
▪ T_2	1(11.1%)	27(62.7%)	
▪ T_3	4(44.4)	10(23.2%)	
▪ T_4	4(44.4%)	1(2.3%)	
N stage			
▪ N_O	6(66.7%)	41(95.4%)	0.094+
▪ N_1	3(33.3%)	2(4.6%)	
Nuclear			
▪ Grade 1	0(0%)	4(9.3%)	0.156
▪ Grade 2	2(22.2%)	32(74.4%)	
▪ Grade 3	7(77.7%)	7(16.2%)	
ESR			
▪ <28	2(22.2%)	22(51.1%)	0.175
▪ >28	7(77.7%)	21(48.8%)	
Stage			
▪ Stage 1	0(0%)	5(11.6%)	0.009**
▪ Stage 2	0(0%)	27(62.7%)	
▪ Stage 3	5(55.5%)	10(23.2%)	
▪ Stage 4	4(44.4%)	1(2.3%)	
UCLA risk			
▪ High risk	9(100%)	10(23.2%)	0.001**
▪ Intermediate	0(0%)	29(67.4%)	
▪ Low risk	0(0%)	4(9.3%)	
SSIGN score			
▪ 0	0 (0%)	3 (6.9%)	< 0.001**
▪ 1-2	0 (0%)	2(4.6%)	
▪ 3-5	0 (0%)	35(81.3%)	
▪ 6-8	7(77.7%)	3(6.9%)	
▪ 9-10	2(22.2%)	0 (0%)	
Histology			
Chromophobe	0(0%)	4(9.3%)	0.158
▪ Clear cell	4(44.4%)	34(79.0%)	
▪ Papillary	3(33.3%)	4(9.3%)	
▪ Sarcomatoid	2(22.2%)	1(2.3%)	
Necrosis			
▪ No	0(0%)	38(88.3%)	<0.001**
▪ Yes	9(100%)	5(11.6%)	
ECOG performance			
▪ 0	0(0%)	24(55.8%)	<0.001**
▪ 1	0(0%)	13(30..2%)	
▪ 2	1(11.1%)	6(13.9%)	
▪ 3	5(55.5%)	0(0%)	
▪ 4	3(33.3%)	0(0%)	

DISCUSSION

52 non-metastatic renal cell carcinoma patients who had radical nephrectomy were all monitored for a year. After a year of follow-up, 43 patients (82.6%) were still disease-free.

Majority of patient's age was between 40 to 60 years with standard deviation of 53.03 ± 14.9 years. 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.*) [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.* [7] demonstrated that young patients, under 40 years old was an independent prognostic factor for the CSS of patients with RCC at five years of follow up.

In contrast to the fact that more than 50% of RCCs are currently diagnosed incidentally (Pantuck *et al.*)

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[6] the majority of patient presentations were symptomatic (82.6%) rather than incidental (17.3%). This indicates that individuals in our study presented to clinicians for therapy later than in other trials that were reported. In contrast to studies that claim incidental tumors are of lower stage and grade, and are less aggressive lesions leading to better patient survival and decreased recurrence, the mode of presentation was not statistically significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value 0.5). As a result, earlier RCC discovery allows for less harmful tumors to be treated, improving the patient's prognosis [8].

Four patients had an inferior venacaval thrombus below the diaphragm but no vein wall invasion, and the majority of patients had T2 stage illness. Several studies show better survival rates for organ-confined disease and document a reduction in survival associated with invasion of the perinephric fat. T stage was found to be a moderately statistically significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value 0.025*).

On univariate analysis, lymph node positivity was found in 9.6% of patients, and it was found to be a significant predictive predictor for disease free survival at 1 year (p value 0.094+). Similar to studies showing that involvement of lymph nodes is related with 5- and 10-year survival rates of 5% to 30% and 0% to 5%, respectively, and is long regarded as a dismal prognostic indication.

Majority of patients had Fuhrmans nuclear grade of 2 (65.3%) (Table 5) and no patient had Fuhrmans nuclear grade 4. At 1 year follow up nuclear grade did not prove significant prognostic predictor 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, Weaver A and Cheville [9].

Majority of patients had clear cell type histology (Table 6) (73. 0%). At one year follow up chromophobe type had 100% disease free survival whereas papillary and sarcomatoid types had 57.1% and 33.3% disease free survival at one year follow up. But type of histology did not prove to be a significant prognostic predictor for disease free survival at 1 year on univariate analysis (p value 0.158). In contrast to other studies present study suggest that clear cell RCC have good prognosis on average compared with papillary, although there are clearly poorly differentiated tumors in each of these subcategories that can be lethal.

Majority of patients had Raised ESR of above 28mm (53.8%) (Table 7) 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*.) [10].

Presence of necrosis was noted in (26.9%) 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 tumor necrosis was an independent predictor of survival in patients with localized disease [11]. Drawback of this parameter comparison was the amount of necrosis was not made out.

Majority of patients had ECOG performance status of 0 (46.1%) 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*. [12]. Majority of patients had tumor stage 2 (51.9%) (Table 10) 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.

Majority of patients had SSIGN score of 3 to 5 (67.3%) 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). Most of patients had intermediate UCLA risk group (55.7%) 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).

Conclusion

Our follow-up guidelines after radical nephrectomy, based on an integrated stage-specific and tumor size protocol, 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 UISS and SSIGN score designs proved to be useful models for assessing prognosis of non-metastatic renal cell carcinoma at one year of follow up.

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