Prognosticfactors in patients with renal cell carcinoma: Is TNM (1997) staging relevant in Indian subpopulation?

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Abstract

BACKGROUND: RCC (Renal Cell Carcinoma) is a common genitourinary malignancy, but its behavior has not been studied in the Indian Subpopulation. **AIMS:** The aim of this study was to assess the validity of 1997 AJCC TNM staging in Indian subpopulation and also to identify independent predictors for survival in patients having RCC. **SETTING AND DESIGN:** Retrospective uncontrolled analysis of patients with RCC was performed at our centre. **MATERIAL AND METHODS:** Medical records of patients of undergoing radical nephrectomy at our center between 1994 to August 2003 were identified retrospectively. Medical records of 178 patients were available for analysis. Patient characteristics, preoperative imaging and surgical details were reviewed. Each tumor was staged according to the 1997 AJCC TNM classification. Nuclear grade was assigned according to the Fuhrman's grading system. **STATISTICAL METHODS:** Statistical analysis was performed using statistical software and descriptive statistics and survival functions were obtained. Univariate and multivariate analysis of factors affecting outcome of the patient were performed. **RESULTS:** Mean follow up period was 42.3 months (range 3 to 108 months). Stage wise 5-year Cancer specific survival was 87.2% in stage 1 disease, 74.3% in stage 2, 36.4% in stage 3 and 3.1% in stage 4. Univariate analysis revealed that stage, grade and lymph node status were statistically significant *(P=0.009, 0.007* and *0.003* respectively). Sub-classifying stage 1 tumors between tumor of less than 4 cm. and more than 4 cm. did not reveal any statistically significant difference in survival *(P=0.32).* Multivariate analysis model revealed that Fuhrman's grade and lymph node status were statistically significant *(P=0.007* and *0.002* respectively). **CONCLUSION:** This study validates the TNM (1997) staging for RCC as having significant survival impact in the Indian subpopulation. Sub-classifying stage 1 tumors between tumor of less than 4 cm. and more than 4 cm is not of much importance. Nuclear grade and lymph node involvement are important independent predictors of survival. Organ confined tumors with high nuclear grades need to be followed up more rigorously.

Key Words: Renal Cell carcinoma, Radical Nephrectomy, TNM staging, Prognostic factors.

Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all malignant tumors in adults. Primary role of surgery in treatment of RCC is related to low radiosensitivety and chemosensitivety of this tumor. Robson was the first to show significant increase in survival rate in patients with RCC who underwent radical nephrectomy.[1] Radical nephrectomy, till now, is the only treatment available which significantly increases survival in patients with organ confined disease.

Pathological stage of RCC is considered to be the most important predictor of survival.[2-4] According to 1997

TNM classification of RCC,[5] T1 disease has been changed from organ confined tumors of less than 2.5 cm in size, to 7 cm. Identification of patients who are at the risk for recurrence is of utmost importance to allow close surveillance and early treatment. Factors other than stage that are considered important in prognosis of RCC are nuclear grade, histological type DNA content and morphometric characteristics of nucleus.[6-10]

With the advent of newer imaging techniques, and more pervasive use of these techniques for various unrelated symptoms, more and more cases are being diagnosed at an earlier stage.[11] It is estimated that more than 50% of cases of RCC in the United States are now being detected incidentally. Most of these incidentally detected tumors are small and low stage and thus have a positive impact on survival of these patients.[12] However in developing countries like India, where these imaging studies are not available widely, most of these patients present with large tumor burden. Therefore in this context, change in size criterion for T1 stage appears appropriate, even though this remains to be analyzed in our population.

The aim of this work was to assess the relevance of the new (1997) TNM staging for RCC in our Indian subpopulation and also to identify independent predictors for survival in patients having RCC.

Materials and Methods

Between 1994 to August 2003, 212 patients underwent radical nephrectomy for Renal Cell Carcinoma at our center. Of these, complete medical records were available in178 patients, which comprised our study population. This study was duly cleared by the ethical committee of our institute.

Patient characteristics e.g. age at the time of surgery, gender, symptoms at the time of presentation viz. hematuria pain, fever, palpable renal mass, weight loss, and presence of varicoceles were evaluated. Preoperative CT and chest X-ray findings were recorded. Operation records were reviewed for the type of surgery performed, tumor size, local extent, lymph node enlargement or any other sites of spread.

Pathological variables assessed included histological subtype, tumor size, extent, lymph node involvement and invasion of renal vein or IVC. After this, each tumor was staged according to the 1997 AJCC TNM classification. Nuclear grading was assigned according to the Fuhrman's grading system.

Statistical Methods

Statistical analysis was performed using the SPSS 10.0 software.

Survival time was calculated from the date of nephrectomy to the last known date of clinical evaluation or death. Survival functions were calculated using Kaplan- Meier product limit method. Difference between individual prognostic factors was evaluated by performing univariate analysis using the Log Rank test. Minimum value for statistical significance was taken as $P=<0.05$. Factors that were found to be significant on univariate analysis were then subjected to multivariate analysis by Cox proportional hazards regression model.

Results

Age of the patients ranged from 22 to 80 years (mean 55.7 ± 11.1 yrs). Male to female ratio was 4.5:1. The most common presenting symptom was hematuria, seen in 78% of the patient. Palpable renal mass was the presenting symptom in 28%, while fever was present in 11.2% of the patients. Other symptoms like loss of weight, varicoceles etc. were present in 14% of the patients. Only 8% of our patients were detected incidentally while being evaluated for unrelated abdominal symptoms.

Open radical nephrectomy was performed 148 patients while laparoscopic radical nephrectomy was done on 24 patients, 5 of the patient had partial nephrectomy. Lymphadenectomy was not performed routinely but enlarged retroperitoneal lymph nodes were excised as a biopsy procedure. The mean tumor size was 9.4 cm (range 4 -20 cm median 8.8 cm) as measured on CECT scan and 9.2 cm (range 3.4 -20 cm median 8.6 cm) on histopathology. TNM (1997) staging was assigned to each tumor. Histological grading was done using Fuhrman grading system. Pathological characteristics of the tumors are listed in Table 1. In Stage 1 tumors, 22.2% tumors were G1, 38.1% were G 2 and 39.7% were G 3.

Mean follow up period was 42.3 months (range 3 to 108 months) Stage wise 5-year Cancer Free survival (CFS) were 87.2% in stage 1 disease, 74.3% in stage 2, 36.4% in stage 3 and 3.1% in stage 4 (Figure 1). Node negative patients had 76.8% 5 year CFS as compared to only 16.8% in node positive patients.

Univariate analysis of the impact of tumor stage, grade, size, lymph node status, presence or absence of systemic symptoms on presentation, on the oncological outcome
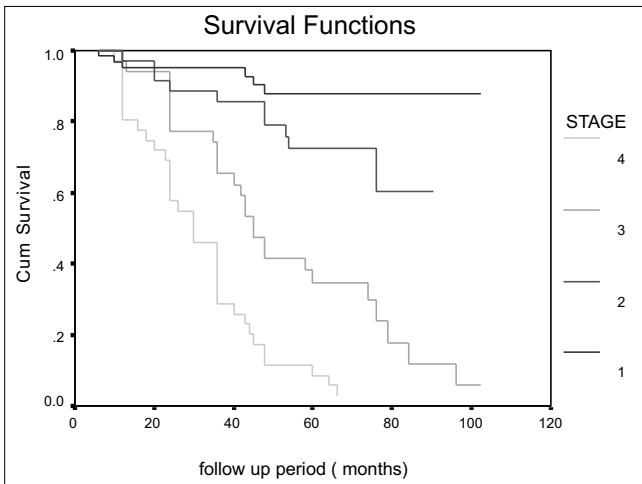
Table 1: Pathological characteristics of the tumor

Pathological characteristics	n (%)
TNM stage	
Stage 1	76 (42.7)
Stage 2	39 (22.0)
Stage 3	34 (19.0)
Stage 4	29 (16.3)
Fuhrman grade	
G1	26 (14.6)
G2	68 (38.2)
G3	63 (35.4)
G4	21 (11.8)
Cell type	
Conventional	114 (64.02)
Papillary	48 (27.0)
Chromophobe	14 (7.86)
Collecting duct	2 (1.12)

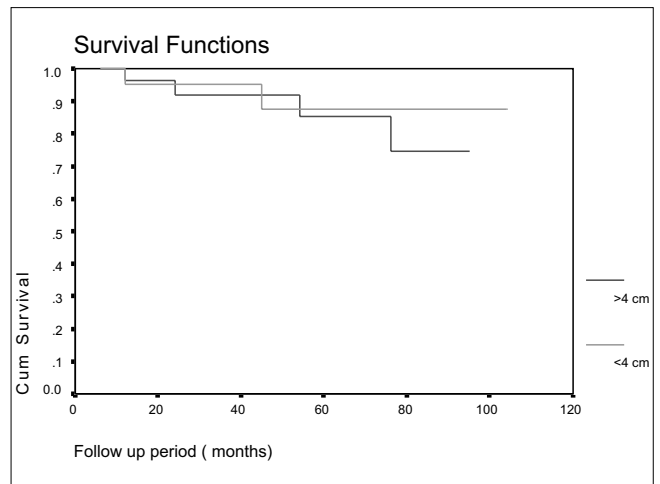Figure 1: Stage wise Cancer free survival probability according to pathological stage (TNM 1997)

Table 2: Univariate analysis of prognostic variables for Cancer Free Survival

Characteristics	Hazard ratio	95% CI (SE%)	P value
Age	0.72	0.25 – 1.43 (3)	0.48
Male gender	0.66	0.18 – 2.12 (4)	0.542
Tumor size (<7cm and >7 cm)	0.47	0.73 - 2.56 (3)	0.32
Systemic symptoms	0.74	0.32 - 1.12 (6)	0.238
Tumor Stage	1.24	0.91 – 2.45 (2)	0.009
Fuhrman's grade	5.45	3.72 - 7.01 (2)	0.007
Lymph node status	6.12	4.21 - 7.05 (4)	0.003

CI: Confidence Interval, SE: Standard error

Figure 2: Survival difference between T1 tumors <4 and >4 cm in size

Table 3: Multivariate analysis of the prognostic variables* for cancer specific survival

Variables*	Category	RR (95% CI)	P-value
Tumor stage	Stage 1-2, Stage 3-4	1.12 (0.87-1.23)	0.090
Fuhrman's grade	G1-2, G3-4	5.76 (3.89-6.78)	0.007
Lymph node status	N0, N1	6.36 (4.79–7.54)	0.003

RR: Relative risk, CI: Confidence Interval, *Variables found significant on univariate analysis

revealed that stage and grade and lymph node status were the factors which had statistically significant impact (*P=0.009,0.007* and *0.003* respectively) (Table 2).

Sub-classifying stage 1 tumors between tumor of less than 4 cm. and more than 4 cm. did not reveal any statistically significant difference in survival *(P=0.32)* (Figure 2)

Multivariate analysis model comparing the effect of tumor size, tumor grade and stage of the tumor using Cox proportional hazard model revealed that Fuhrman's grade and lymph node status had statistically significant impact on survival (*P=0.007* and *0.002* respectively) (Table 3).

Discussion

In 1997 AJCC/ UICC increased the size cutoff for T1

tumors from 2.5 to 7 cm[5]. This change, as well as the significance of size in predicting the behavior of RCC has been controversial. In one study, 209 patients of RCC, no prognostically significant cut off size was identified in tumors confined to the kidney.[13] Similarly other studies[14,15] also have shown no significant correlation between the tumor size and prognosis. On the contrary Hafez et al[16] showed significant difference in survival in tumor <4 cm and >4 cm. in size. They proposed sub classifying T1 tumors as T1a and T1b as <4 cm and >4 cm respectively. Similar results were

obtained by Zisman et al,[17] Igrashi et al.[18] In fact the 2003 UICC TNM classification has withheld this change and sub classified T1 stage as T1a being <4 cm and T1b being 4 to 7 cm tumors.[19]

In concordance with 1997 TNM staging, the present study revealed a significant difference in oncological outcome in T1 and T2 tumors; 87.2% 5 year CFS in stage 1 and 74.3% in stage 2 *(P=0.041)*, thus upholding the change in the 1997 TNM staging. However sub classifying the T1 tumors to <4 and >4 cm did not reveal any significant difference in survival.

Multivariate analysis of the present subgroup revealed that only the Fuhrman's nuclear grade had significant independent predictive value for the outcome of the patient. In Fuhrman's original report nuclear grade proved to be to be the most significant prognostic factor for stage 1 cancers.[20] Other studies of Fuhrman grade, as well as other grading systems.[5,7,20-22] have identified nuclear grade as an independent variable for determining patient's outcome. Present literature recommends an yearly follow up for organ confined disease regardless of the grade of the tumor.[23] Considering a more aggressive behavior, it may be prudent that tumors with high nuclear grade be followed up more rigorously (probably 6 monthly) in the postoperative period.

In the present study, the stage wise cancer free survival has been lower than the survival reported in the western literature. In recent literature, the 5 year survival for stage 1 tumors have been around 90 - 100%, 75 to 90% in stage 2, 60 to 70% in stage 3 and 15 to 30% in stage 4.[24] The explanation for this observation is difficult to derive from the present study design but interestingly large proportion of the malignancy were of higher grade (14.8% G 1, 38.1% G 2, 35.2% G 3 and 11.9% G 4).Even in stage 1 disease 39.1% of the patients had G 3 tumors. It has been observed in other studies that as the tumor size increases, the likelihood of malignant and aggressive behavior of the tumor increases.[25] The mean tumor size in the western studies is smaller (6.5 - 7 cm)[26,27] as compared to our study group (Mean tumor size 9.2 cm.), maybe the larger tumor size in our subpopulation portends a worse prognosis for our patients. Other causes can be a poorer general condition of our patients or possibly the tumor behavior being more aggressive than the western counterparts.

Lymph node involvement has been well documented to significantly affect the survival. Literature reports 5-year cause specific survival in node positive disease to be only 8-35%.[6,26,28] In our experience also, lymph node involvement augured a poorer cancer specific survival.

Conclusion

This study validates the TNM (1997) staging as having significant survival impact in the Indian subpopulation harboring Renal Cell Cancer. In these patients nuclear grade and lymph node involvement are important independent predictors of survival. Our patients of stage 1 disease have higher nuclear grades which may explain the relatively poor survival. Hence such patients with high grade tumor should be followed up more rigorously. Size of the tumor does not have independent impact on survival and considerations for reducing the size cutoff to 4-5 cm does not appear to be necessary.

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