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Impact of Charlson's comorbidity index on overall survival following tumor nephrectomy for renal cell carcinoma

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Abstract
Objective To study the impact of Charlson's comorbidity index on overall survival following radical and partial nephrectomy performed for renal cell carcinoma (RCC).
Methods Patients with primary RCC treated by tumor nephrectomy with at least 1 year of follow-up were included. The outcome parameters assessed were overall survival, impact of surgery on quality of life of patients using Karnofsky's index and correlation of survival with respect to comorbid conditions, using Charlson's index comorbidity score, grade and stage of disease.
Results A total of 214 tumor nephrectomies were performed during study period, of which 157 (73%) fulfilling the criteria were included in the final analysis. The mean age at presentation was 57 ± 12 years. The mean Charlson's index was 2.89 ± 2.22. Tumor stages were I–IV in 33, 30, 16 and 21%, respectively. The overall survival was 65% at a mean follow-up of 39 ± 5 months. The mean pre op Karnofsky's index was 79.5 ± 7.13 and at follow-up it was 95.41 ± 10.65 ($P < .001$). The difference in functional status of patient (Karnofsky's Index) for every stage including Stage-IV was statistically significant (P 0.01). Survival analysis showed a significant differences in overall survival according to stage (P 0.001), grade (P 0.001), size of tumor (P 0.001) and Charlson's index ($P = 0.05$).
Conclusions There was significant improvement in the quality of life, following tumor nephrectomy, even for Stage-IV cancers. Multivariate analysis indicated besides tumor stage, grade, and size of the tumor, Charlson's index has a significant predictive value on overall survival.

Introduction

The estimated new cases of kidney cancer in 2008 in United States were about 54,390 with an estimated mortality of 13,010 [1]. The cancer survival following definitive treatment has traditionally focused on the gross and microscopic characteristics of the tumor. In advanced renal cell carcinoma (RCC), known clinical factors associated with outcome include disease-free interval, number of metastatic sites, and several laboratory variables such as hemoglobin, calcium, and lactate dehydrogenase besides performance status. In an analysis of the SEER database, the impact of gender in renal cell carcinoma was assessed by Aron and colleagues [2]. They noted that men were present with larger, higher stage, higher grade RCC than women. Overall survival is better in women, whereas cancer-specific survival is not significantly different.

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Comorbidity is an important consideration in oncology practice, particularly among older patients. The overall health of patients can also affect survival. Most of the urological malignancies are seen in geriatric patients, survival factor should also take into account the coexisting medical conditions. Majority of patients with RCC were present in the 6–7th decade. It is recently noted that despite surgical therapy, competing-cause mortality for patients with renal masses rises with increasing patient age [3]. After 5 years, one-third of elderly patients (≥70 years) will die because of other causes [3]. This necessitates studies to evaluate the role of active surveillance as an initial therapeutic approach for some small renal masses. In a recent paper, Berger et al. [4] noted that comorbidity is an independent prognostic factor for OS in patients with renal cell carcinoma. Capturing the comorbidity information using validated instruments can improve the preoperative evaluation of patients by providing more accurate prognostic information.

As significant proportions of patients' with RCC have other medical conditions, it is important to explore the effect of preexisting medical disease on survival after definite surgical treatment. The aim of the present investigation was to explore the relevance of comorbid conditions on the overall survival in a cohort of patients with RCC treated by partial and radical nephrectomy.

Methods

This was a retrospective analysis of data over a period of 13 years from January 1995 to October 2007. The clinical and pathologic data of all patients treated by partial or radical nephrectomy for RCC were reviewed. Patients with renal tumor other than adenocarcinoma, whose surgery was done in an outside hospital, incomplete/missing medical records, failure to follow-up were excluded. The final study population consisted of 157 patients with RCC who had undergone radical or partial nephrectomy. The clinical, biologic, and diagnostic data were collected. Stage of tumor at diagnosis, histological tumor size (largest diameter), p TNM stage (TNM-UICC 2002 [5]), Fuhrman nuclear grade, and microscopic vascular invasion were also assessed. The Fuhrman nuclear grade was defined as I, II, III, and IV. Follow-up outpatient clinics were scheduled 1 month after surgery, then clinical and imaging evaluations every 6 months to 1 year for localized disease and every 6 months for more advanced stages were carried out. For each evaluation, the following criteria were recorded: the patient's status (alive or dead with cause of death) and progression or without progression, thereby enabling the interval before progression to be determined.

Comorbidity was objectively evaluated by using the Charlson's comorbidity index [6]. This involves a method for classifying comorbid conditions that might alter the risk of mortality for use in longitudinal studies. It is a weighted index that takes into account the number and the seriousness of comorbid disease. The comorbidity information was obtained by review of the medical records. Comorbidity was defined as preexisting medical conditions present at the diagnosis of cancer, including previous or synchronous cancers. In the Charlson's index, specific diseases are graded into one of three levels of severity: low (Charlson's score 2 OR<), moderate (Charlson's score 3–4), and severe (Charlson's score 5 OR>) according to the level of individual organ function and prognostic importance.

Quality of life was assessed both pre- and postoperatively (at 1st month follow-up) using Karnofsky's score [7]. BMI was determined and categorized into 5 categories: normal (18.5–24.9), over weight (25–29.9), obesity Class I (30–34.9), obesity Class II (35–39.9), and obesity Class III (>40).

Statistical methods: Qualitative variables were compared using a 2×2 test, and Student t test was used to compare quantitative variables. Overall survival, specific survival, and progression-free survival curves were obtained for both age groups using the Kaplan–Meier method and were compared using a log-rank test. Univariate and multivariate Cox regression analyses were performed to evaluate the relationship between disease-specific survival and gender, TNM pathologic stage, RCC histological type, tumor grade, tumor size (continuous variable), incidental or symptomatic disease, and in addition to other variables, age, Charlson's comorbidity index and quality of life using Karnofsky's index. The different tests were used with a risk of $P < 0.05$.

Results

The mean age of the population was 57 ± 12 (25–81 years). There were 29% women and 71% men.

Table 1 Difference in the functional status (as determined by Karnofsky's index) before and after nephrectomy

Stage	Number of patients	Pre op Karnofsky	Post op Karnofsky	*P*-value
I	50	81.8 ± 6.6	98.6 ± 3.5	
II	44	79.32 ± 6.95	97.27 ± 7.2	<0.001
III	30	79.0 ± 6.07	95.67 ± 7.27	
IV	33	76.6 ± 1.42	87.88 ± 18.3	0.013

The mean ages of men and women were 54.84 ± 13.11 and 57.58 ± 11.74, respectively, which was not statistically different ($P = 0.173$). The BMI indicates that about half (48%) were normal, one-third were over weight, and 14, 4 and 1% were of Class I–III obese. There were 33, 30, 16, 21% patients in Stages I–IV, respectively. Majority of tumors were clear cell type (85%); papillary constitutes 10%, chromophobe 3%, and 1% each of collecting duct and unclassified. The Fuhrman's grading indicates that there were 23, 53, and 24% in Grade I–III, respectively. The mean Charlson's score was 2.89 ± 2.22, score of ≤2 was noted in 48%, 3–4 in 36%, and 5 or more in 16%. The mean pre- and postoperative Karnofsky's scores (Table 1) were 79.5 ± 7.1 and 95.4 ± 10.6 ($P < 0.001$), respectively.

The mean follow-up was 39 (15–67) months for all patients. The OS rate was 65%. The relationship between the severity of the comorbidity and the OS is illustrated with a Kaplan–Meier survival curve (Fig. 1). A clear prognostic gradient can be seen for patients with severe comorbidity (5 or more score) compared to the groups with a score of 2 and 3–4. We did not find any impact of BMI on survival of patients with renal cell carcinoma on a univariate analysis (P 0.12). The overall survival was better in women with odd ratio for risk estimate = 2.35 (1.05, 5.22). The effect of moderate and mild comorbidity was less clear, although the overall relationship of the severity of comorbidity and survival was significantly different (log-rank _ 2 12.84; P _ .005). On univariate analysis, age, comorbidity, tumor size, Fuhrman's grade, and pathologic stage were predicted for OS. Multivariate Cox proportional hazards analysis (Table 2.) showed that besides clinical stage and grade, Charlson's comorbidity index was significant for scores ≤5 and >5.

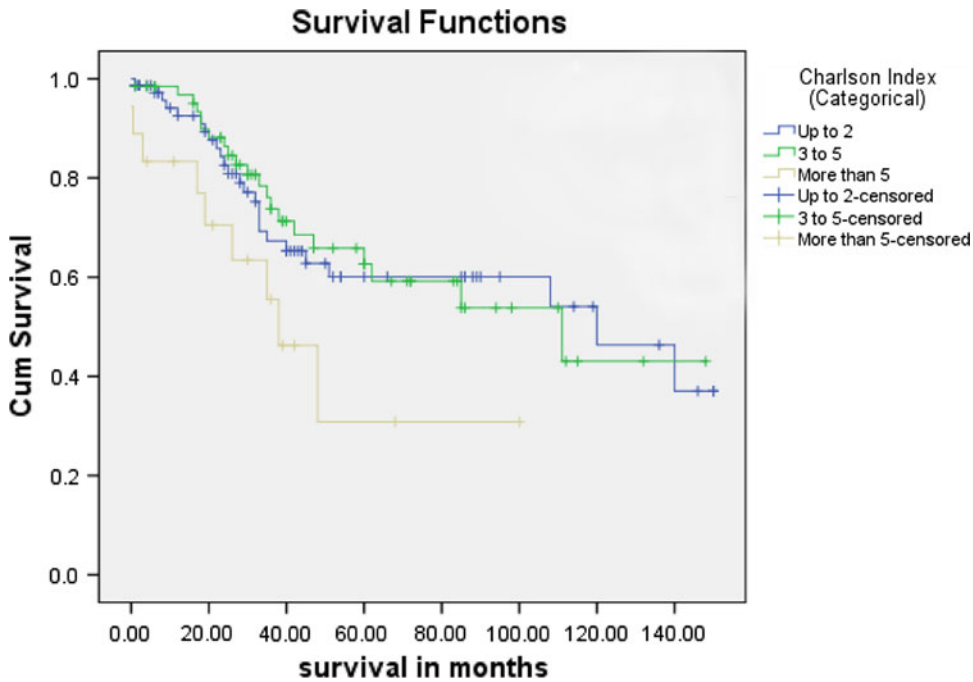

Fig. 1 Kaplan–Meier survival curve indicating the difference in overall survival of patients with mild, moderate, and severe comorbidities

Table 2 Multivariate analysis of grade, stage, and Charlson's index on overall survival

Characteristics	Adjusted relative risk	95.0% CI for adjusted relative risk		*P*-value
Clinical stage				
Stage-I	1†			
Stage-II	0.6	0.2	1.6	0.30
Stage-III	2.1	0.9	5.0	0.10
Stage-IV	4.6	2.1	9.8	0.001
Grade of tumor				
Grade-I	1†			
Grade-II	2.1	0.7	6.1	0.20
Grade-III	7.2	2.3	22.3	0.001
Charlson's score				
<5	1†			
≥5	2.0	1.0	4.1	0.05

† refers to "reference point for multivariate analysis"

Discussion

In the current work, we examined the effect of comorbidity on OS and found that comorbidity, in addition to age, stage, and grade, predicted for OS in patients undergoing radical or partial nephrectomy for RCC. Assessment of comorbidity is part of preoperative work to determine patients' ability to tolerate surgery and/or whether a patient will benefit from surgery; this information has not been formally integrated into the assessment of survival after surgery.

Aron and colleagues [2] evaluated the impact of gender in renal cell carcinoma using the SEER database and noted that men present with larger, higher stage, higher grade RCC than women. Overall survival is better in women, whereas cancer-specific survival is not significantly different. Our own data indicate that OS was better in women than in men ($P = 0.04$), with men having less survival, and odd ratio for risk assessment was 2.35. Woldrich et al. [8] analyzed patterns of disease presentation and outcome of renal cell carcinomas by gender using data from the National Cancer Database during a 10-year period. A ratio of 1.65 of renal cell carcinoma for males compared to females was found. Women are more likely than men to have Stage-I tumors. Both men and women have demonstrated stage migration, although women more so than men.

Population studies link increased BMI with an increased risk of cancer and cancer mortality, and in particular a greater risk of RCC. We evaluated the impact of BMI and other clinical/pathological characteristics on survival in patients with RCC that treated with radical or partial nephrectomy. Donat et al. [9] noted that although an increased BMI was associated with a greater proportion of clear cell histology, comorbidity, and surgical morbidity, BMI did not adversely impact overall or progression-free survival. However, the impact of BMI is controversial as Kamat et al. [10] found that overweight and obese patients with renal cell carcinoma have a more favorable prognosis than patients with a normal BMI. However, this requires confirmation by studies from different centers that a high BMI confers a survival advantage to patients undergoing nephrectomy before BMI could be considered an important prognostic factor in renal cell carcinoma. The data from current work did not indicate BMI to be an important prognostic factor in patients with RCC undergoing tumor nephrectomy.

Both quality of life (QoL) and comorbidity influence therapy and prognosis in cancer patients. By using the age-adjusted Charlson's comorbidity index (ACCI), Koppie and colleagues [11] characterized the impact of age and comorbidity on disease progression and overall survival after radical cystectomy (RC) for transitional cell carcinoma of the bladder. They noted that age and comorbidity among patients who underwent RC at a cancer referral hospital increased with time. Both age and comorbidity were associated with treatment selection and

survival and should, therefore, be considered when comparing outcomes after RC.

In a recently reported work [12], it was noted that a significant differences in overall survival according to stage ($P < 0.001$) and Charlson's index ($P = 0.02$), between localized stages and locally advanced or metastatic stages ($P < 0.001$) and between patients with a Charlson's index of 2 or less vs. greater than 2 ($P < 0.001$), particularly in those with local stage ($P < 0.001$) but not in those with locally advanced or metastatic stage ($P > 0.05$). Gettman and colleagues [13] noted that the Charlson's index did not predict cause specific survival in a cohort of surgically treated patients with tumor thrombus. They found that characteristics of the primary tumor remained the most important predictors of cause-specific survival in this cohort.

There are a few limitations of the current study. First it is a retrospective study with potential bias in assessment of both comorbidity and functional status of patients as determined by Charlson's score and Karnofsky's index. However, only those records were selected from which complete record of patients' status and functional abilities could be obtained. Moreover, the sample size was relatively smaller for large duration of study recruitment. This is also explained by the strict inclusion and exclusion criteria.

In conclusion, the results of our work indicate that severe comorbidity (>5 Charlson's index) shows an inclination toward statistical significance and independent predictor of OS in patients undergoing radical or partial nephrectomy for RCC. This demonstrates that OS is dependent on not only tumor-specific variables (i.e., pathologic stage and grade) but also patient-specific variables (i.e., comorbidity, gender, and age). These factors should be taken into consideration in the preoperative assessment as important factors predicting the outcome. Recording comorbidity information with a validated instrument like Charlson's index has a potential to improve the preoperative evaluation of patients by providing more accurate prognostic information.

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