Survival and prognostic factors in renal cell carcinoma in Saudi patients: A ten year review

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ABSTRACT
Objectives: To study the survival pattern and prognostic variables that influence the management outcome of Saudi patients with renal cell carcinoma (RCC). Patients and methods: A retrospective review of 32 Saudi patients with renal cell carcinoma was carried out. Kaplan-Meier curves were used for survival analysis. Age, sex, clinical presentation and pathological features of the tumors were analyzed for their significance as prognostic factors using the multivariate analysis by Cox proportional hazard model. Results: The group comprised 18 male and 14 female patients with a mean age 50.9±14.5 years. Patients with stage I, II and IIIa disease had a 5 year survival of 95% in comparison to 15% for stage IV disease: this marked difference in survival was statistically significant (p=0.0001). The survival was also significantly different according to tumor size (p=0.005); the 5 year survival was 95% for patients with tumors less than 10 cm in size compared to 25% for patients with tumors greater than 10 cm. Two important and independent prognostic variables were noted using the Cox proportional hazard model: the anatomic extent of the tumor (p=0.02) and the tumor size (p=0.033). Conclusion: Our study affirms that the stage of RCC at presentation is the most important prognostic factor affecting the survival of patients. Size of the tumor was also important and independent prognostic variable.

Keywords: Carcinoma, renal cell, nephrectomy.

Renal cell carcinoma (RCC) is the most common renal parenchymal tumor in adults. The anatomic extent of the tumor at the time of surgical intervention has been the most constant single variable identified in determining survival. Other possible prognostic factors which have been the subject of various reports include nuclear grade, cell type, tumor size, the age of the patient at diagnosis, sex and clinical presentation. An increasing number of RCC patients are being diagnosed incidentally with favorable prognosis in comparison to the symptomatic patients. Clinical studies documenting survival and prognostic factors in patients with RCC in Saudi Arabia are lacking. This review was designed to look at the survival pattern of Saudi patients with renal cell carcinoma that were treated at the Urology Unit, King Khalid University Hospital (KKUH) and at prognostic variables that influenced the outcome of their treatment.

Patients and methods. Seventy eight patients were diagnosed and managed for renal tumors in the period between June 1986 and 1996 at KKUH. Thirty six patients were non Saudi and were excluded from the final analysis because of their diverse ethnic origin; adequate follow up was also lacking in this group because most of these patients were not permanent residents of Saudi Arabia and presumably went back to their native countries after treatment. Ten Saudi patients were excluded because they were found to have renal tumors other than RCC on histological examination of their removed kidneys.

The clinical histories of the 32 Saudi patients with renal cell cancer were examined. Various characteristics believed to be associated with RCC were recorded for subsequent analysis. These included age, sex, presenting symptoms and signs, duration of symptoms, laboratory findings, pathological stage, tumor size, laterality, cell type and grade. Routine blood count and chemistry, liver function tests and urinalysis were carried out on all patients. Tumor diagnosis and staging was carried out by intravenous pyelogram or ultrasound, chest roentgenography, computerized abdominal tomo-
Table 1 - Tumor stage and size

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Average size</th>
<th>No. of patients</th>
<th>Average size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>Incidental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13</td>
<td>7.9</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>8.5</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>IIIa</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>77</td>
</tr>
<tr>
<td>IIIb</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
<td>7.3</td>
<td>2</td>
<td>11.4</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>7.7</td>
<td>10</td>
<td>8.2</td>
</tr>
</tbody>
</table>

graphy (CT) and bone scan. Renal arteriograms were carried out as indicated.

Tumor staging of RCC was classified according to Flock's and Kadesky (1958). Stage I: tumor confined to the kidney, stage II: tumor invading perirenal fat but confined by Gerota's fascia, stage IIIa: tumor in renal vein or inferior vena cava, stage IIIb: Tumor in lymph nodes and stage IV: involvement of adjacent organs or distant metastasis.

All patients in stage I-III underwent radical nephrectomy which was the standard operative procedure except for one patient with bilateral synchronous stage I disease who had bilateral partial nephrectomy. Two patients with extension of the tumor thrombus into the abdominal part of their inferior vena cava had cavotomy and thrombus extraction added to the procedure. Patients in stage IV with systemic metastasis were not operated on except for one patient who had solitary metastasis to the conalateral adrenal; this patient had nephrectomy and contralateral adrenalectomy. Two patients in stage IV had involvement of adjacent structures; one into retroperitoneal cysts where all tumor tissue was successfully excised; the other patient had inoperable tumor due to infiltration into the posterior abdominal wall. No adjuvant therapy was given to these patients. Complete follow up information was available on 31 patients.

In the analysis of the data; statistical methods used the Kaplan-Meier curves for survival analysis, log rank tests and multiple regression procedures of Cox.

Results. The group in this review comprised 18 males and 14 females (M:F ratio 1.2:1) with a mean age of 50.9±14.5 years (range 17-85). Duration of symptoms varied widely from few months to few years. The most common presenting symptoms were loin pain (48%) and hematuria (33%). Two patients presented with the so called “classic triad” of loin pain, hematuria and renal mass. Ten patients (31%) were diagnosed incidentally using ultrasound during investigations of non urological problems. Non specific presenting symptoms such as weight loss, fever, hypertension, anemia and varicocele were rarely encountered. No case of ectopic hormone production was identified.

Nineteen tumors occurred on the right side, 12 on the left side and one patient had bilateral synchronous tumors. Table 1 shows the number of patients in each stage and the average size of the tumor for symptomatic as well as incidental RCC. Histological examination of the 28 resected tumors showed cell typing as clear cell in 15(53.5%), granular cell in 6(21.5%) and mixed cell type in 7 (25%). Tumor grade was available only on 10 patients and it’s significance could not be tested.

One patient was lost to follow up before 1 year. The longest follow up was 120 months with a mean follow up of 33 months. Twenty three patients are still alive; one with metastasis to the shoulder. One patient died of non cancer related illness and seven died of their renal cancer. The patient in stage IV with extension of RCC into the retroperitoneal cysts is still alive four years after surgery with no evidence of tumor recurrence. All other patients in stage IV were dead within 6 months of the diagnosis except for the patient with solitary metastasis to the adrenal who survived for 24 months before succumbing to his illness.

The survival rate at 5 years for patients with stages I-IIIa using censored data was 95% compared to 15% for patients with stage IV (Fig. 1). This difference was statistically significant (p=0.0001). There was also significant statistical difference in survival at 5 years between patients with tumors less than 10 cm and those greater than 10 cm (Fig. 2). We could not demonstrate any significant survival advantage in patients with incidental RCC when compared to patients with symptomatic tumors.

The various possible prognostic factors recorded in this review were analyzed for their significance using the Cox proportional hazard model. We found two important and independent prognostic variables: the anatomic extent of the tumor (p=0.02) and the size of the tumor (p=0.033). All other variables tested were not significant.

Discussion. This study demonstrates the importance of the anatomic extent of the tumor as a prognostic variable in predicting survival in patients with renal cell carcinoma. Stages I, II and IIIa are potentially curable;5 the disease being amenable to complete surgical excision. Boxer and associates found no difference in survival among patients with stages I, II and III provided the lymph nodes were not involved.6 Several investigators have reported that renal vein involvement, even with extension into the inferior vena cava, when not associated with regional lymph node involvement, does not significantly alter
the prognosis compared with stage I. The disease process, in stage III and stage IV, is systemic in nature and beyond cure in the absence of effective adjuvant therapy. Libertino and associates could not demonstrate significant differences between these two groups in terms of survival. The five year survival of patients with stages I and II range from 51% to 93% in different reports; and 33.5% to 80% for stage III. All the patients but one in stages I, II and III in our group are alive with an overall survival rate of 95% at 5 years. Although not all patients in our group were followed up for a minimum of 5 years, the use of the Kaplan-Meier survival curves gives an accurate estimate of survival probability. Life tables account for variations in patients follow up and utilizes censored data that takes into account cancer related and non cancer related deaths. The apparent enhanced survival in Saudi patients with RCC (stages I-III) may be due to local tumor-host factors; the other explanation may be the absence of patients with stage III from our group of patients.

RCC patients in stage IV have a dismal prognosis with 5 year survival rates of 5% to 10%. Eighty percent of patients with metastatic disease at the time of nephrectomy are dead within 2 years of their operation. These facts are in accordance with our findings; they form the basis for not operating on patients with metastatic disease. The palliative relief of symptoms does not require nephrectomy; adequate analgesia and local radiotherapy can control pain while angioinfection of the tumour can be used for control of hematuria. Skinner and associates recommend an aggressive approach to solitary metastasis in carefully selected patients. We found this recommendation of value in 2 of our patients with stage IV and solitary metastasis to the adrenal or retroperitoneal cysts.

The impact of tumor size on the prognosis of patients with RCC is a controversial issue, many studies fail to account for stage and grade when evaluating the significance of tumor size. Giuliani et al found significant difference in survival at 5 years when comparing patients with tumors less than 10 cm. This is in accordance with our findings. Furthermore, we found tumor size to be a significant and independent variable when tested using the Cox proportional hazard model.

The favorable impact of female gender on patients with RCC has been proposed by some investigators; this view has been contested by other studies. The difference in survival between sexes seems to diminish when results are stratified according to stage and grade. Likewise investigators have found that a younger age at diagnosis did not have an adverse effect on survival. The role of various presenting features and duration of symptoms as prognosticators for survival of patients with RCC is controversial. None of these clinical variables adversely affect the survival in our group of Saudi patients. Granular cell on histological examination of RCC is thought to carry a worse prognosis than clear cell; Other investigators found this not to be the case. It was difficult to examine the prognostic value of cell type and grade on the different stages in our group since all patients but one in stages I, II and II are alive. The cell type in patients with stage V was lacking in most patients since nephrectomy was not carried out and postmortem examinations are not routinely carried.
out in Saudi Arabia.

There has been a dramatic increase in the frequency of incidental RCC in recent years. Improved survival was noted in incidental tumors in comparison to symptomatic ones on account of lower stage, grade and tumoral size of incidental renal cancer. We did not find that incidental tumors carry a favorable prognosis, possibly because of the high percentage of stage IV (20%) patients in comparison to other reports. Although, the improved survival noted for incidental renal cancer is maintained when stage to stage comparison is carried out; we did not find any difference since all but one patient in stages I to III are alive in this review. It remains to be seen whether differences in survival will become apparent between these groups on longer follow up.

In conclusion, our study affirms that the stage of RCC at presentation is the most important prognostic factor affecting the survival of patients. Size of the tumor was also important and independent prognostic variable. Larger series with longer periods of follow up are needed to ascertain the survival pattern and prognostic variables in Saudi patients with RCC.

References