# Factors Influencing Prognosis in Renal Cell Carcinoma

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## Introduction

Renal cell carcinoma (RCC) is unique in many aspects, Firstly, its response to chemotherapy, radiotherapy and hormonal manipulation is extremely poor leaving surgical extirpation as only effective means of treatment. Secondly, sometimes secondaries regress after removal of the primary tumor indicating unusual response to host defense system once tumor burden is reduced. RCC's unpredictable behavior also results from the fact that it often shows long term survival inthe presence of metastasis, spontaneous regression[1] and late recurrences[2]. All these factors make prediction concerning the behavior of RCC extremely difficult. The various parameters used to define response of RCC are not as clearly outlined as for certain other neoplasms.

Although there had been tremendous progress in our understanding of the tumor biology, post operative biological behavior of RCC remains elusive. Factors which influence the clinical behavior of an individual patient is related to the inherent properties of the tumor, host response and the treatment offered. As the last two parameters are usually obvious, various investigators have attempted to identify morphological, pathological, clinical and demographic feature to predict the survival in patient treated for RCC surgically.

## Clinical Stage

Clinical/pathological stage is the single mose important determinant of prognosis in patients with RCC. Regardless of the staging system used patients with organ confined disease (Stage I orTl-2NOMO) have a five year survival of 60-90%, survival curve slopes down with increasing stage of the disease. Effects of renal vein and inferior vena caval involvement on prognosis are controversial. Some believe that it adversely affects the survival[3]. Whereas other[4] contends that if other factors (perinephric fat, and lymph node involvement) are excluded and the staging is adjusted, presence of thrombus inthe renal vein per se does not incurany added disadvantage[5]. Vena caval wall invasion, however, has a detrimental effect on the prognosis if the tumor resection is not complete with part of the normal caval wall. Patients with cavalthrombus are morn likely to develop hepatic and uretenc metastasis than bone or brain metastases probably resulting from alteration in the routes of the lymphatics[6].

Separate staging is not done mfor renal pelvis invasion in either of the systems, though review of the reported data reveals a significant difference in the 5 year survival between tumors confined to the renal parenchyma (82%) versus tumor invading the renal pelvis (50%). Siminovitch et al[7], however, reviewed the prognostic importance of the renal pelvis invasion in 241 patients with nephrectomy for renal cell carcinoma and concluded that renal pelvis invasion per se has no significant impact on prognosis. Many investigators have reported a difference in the survival curves of stage I and II patients. These probably indicate the importance of perinpebric fat involvement. Skinner et al[4] have reported a difference in the 5 year disease specific survival of 65% and 47% respectively for stage I and 11. This difference is further accentuated in 10 year survival rate of 56% and 20% respectively. Indicating the difference between a tumor confined to the cortex and the one that has affected the medulla as well.

Patients with metastatic disease have a dismal prognosis as there is no effective means of curing besides removal of the primary. Various studies have reported an overall 5 years survival for patients

with metastatic disease at 5-10%[8] and 10 year surival of 0-7%[4] Skinner[4] has reported better survival for patients with grade IV disease with single metastatic lesion that is removed, surgically. However, similar results have not been reported for patients with nodal involvement, who have undergone surgical lymhadenectomy at the time of radical nephrecomy[8]. Libertino compared the survival in two groups of patients one that has undergone lymphadenectomy and the other that has not and found no significant difference. Bassilet al[8] compared in a retrospective study 5 year survival in 252 patients who had radical nephrectomy for renal cell carcinoma in first group of 100 patients who bad radial nephrectomy alone without lymph node dissection 5 year survival was 59% whereas in the second group of 133 patients inwhorne radical nephrectomy was perfonned along with lymph node dissection was slightly better 65%, but not statistically significant. Thus lymphadenectomy at the time of radical nepbrectomy is controversial, although theoretically it may be of some help in patients who have disease confined to the nodes that are surgically removed as part of radical nephretomy. Inovlvement of lymph nodes, however, indicates systemic disease with a likelihood of distant metastases and failure to render patient free of micrometastases. Metastatic renal cell carcinoma has poor prognosis with a 5 year survival of under 10% and 10 year survival between 0 to 7% in various studies[4,10]. This results from failure in evolution of adjuvant therapeutic options for RCC. Patients with grade IV metastatic disease with solitaiy metastatic lesion amenable to surgical resection defy the generally held low survival in these patients. Skinner et al and Middleton RJ “, reported a five year survival of 29% and 35% respectively after surgical excision of single metastatic lesion.

**Histological factors**

Various histological parameters including morphological characteristics, cell type, cell necrosis, tumor demarcation from normal tissue and nuclear grading have been used to grade RCC. Various grading systems exist those correlate histological characteristics to survival. Medeiros and coworkers[12], describe relationship of survival to nuclear grade and concluded that increasing grade decreases the survival though statistical difference between grade 1 and 2 was insignificant.
Various cell types of RCC include clear, granular, spindle and mixed. Cell type has also been described to correlate with disease free survival. Most investigators agree that spindle cell variety of RCC has the most ominous prognosis[13,14], but opinions concerning other cell types differ. Lieber et Al[14], found no difference in survival among young patients with clear or granulat cell types. Opinion concerning mixed cell type is that the prognois is better than spindle but worse compared to clear or granular. Concerning the histological pattern various authors have reported correlation between histological type and disease free survival. Mancilla-Jimenez eta[11] , have reported a singificantly better survival for patients with papillary architecture than other histological varieties including tubular or cystic. In contrast Skinner et al[4], have reported no significant difference in the various histological types. Similarly, Boxer et al[13], have made similar observations.

**Miscellaneous factors**

Factors like demographic and clinical characteristics, pathological stage, nuclear grade and cell type, tumor size, histologic pattern, DNA content have well-established significance in predicting the prognosis though their relative importance is still debatable. Recently progress in cytogenetics has enabled us to identify certain oncogenes, which can cause or contribute to the development of RCC[16]. Definition of prognostic indices is clouded by difficulty in agreeing for a standardized staging system and histological parameters. At present two staging systems are in common use, Robson’s and Tumor,

node and metastasis (TNM). Robson's staging is still in wide spread use though it is often criticised for grouping lymphatic and venous involvement in stage III . The detennental effectoftheformeronprognosis is well established while that of the later is doubtful. Several investigaors have shown that prognosis with renal vein and even inferior vena caval, involvement when not associated with perinpehric fat and lymph node involvement, is not different from stage I tumor[13,9]. . On the other hand staging of tumor in TNM system has the advantage of classifying patients into prognostically reliable groups and also has the potential of substratifying them. Many histological characteristics of renal cell carcinoma have been described and they are grouped in different histological grading systems. They all have similar portential in predicting the prognosis. It is therefore, advisable that each hospital should have a single histological grading system, so that results could be compared even after long period of time.

Though isolated cases of long term survival, in patients with metastatic disease, have been reproted in the literature' generally survival curves forpatients of various stages display consistency[17]. Five year survival for patients with metastatic disease is among 0-11%[12]. It is, however, difficult to define as to which patients will do well, though some features as young age at presentation, female sex and metastases confined to lungs and a low grade of primary tumor, all confer better prognosis.

Nephrectomy in patients with rnetastatic disease had been discussed in various studies. Generally, the opinion is that as prognosis is very poor, radical procedure could be avoided except for patients who are fit with minimal co-morbidities. Some studis have reported improved survival butbetter survival could just be a result of improved prognosis in patients who are operable. Even the operative procedure for RCC is controversial.Many investigators have challanged the need for performign radical nephrectomy as simple nephrectomy results are comparable. Although Robsonetal[18] was convinced that radici nephrectomy gives better results than simple, the two have not been compared in a controlled trial.

RCC like many other solid tumors is unpredictable in its outcome, though may universally held features differentiating between tumors of good and dismal prognosis are true for RCC occasional atients confounds the statistics. Many of the unanswered questions concerning RCC like, a) Is radical cystectomy any better than simple, b) When and in whome lymphadenectomy is indicated, c) does nphron sparing surgery a worthwhile option in patients with bilateral renal cell carcinoma and in tumors in anatomically and physiologically single kidneys.

The extent of the primary tumor is the single most important factor affecting the prognosis. Renal vein involvement alone does not confer any aditional risk in otherwise organ confined tumor. Regarding clinical factors and other miscellaneous variables like hypercalcemia, eiythrocytosis, increased ESR etc. one can say that they are indicators of metastatic disese and imply poor outcome. Nuclear grading and cell type are important in tumors that have spread beyond the confines of surgical resection and indicate biological behavior of the tumor. Long term follow-up is important as late appearance of metastases is not an entirely unknown phenomenon in RCC; 6 monthly chest x-ray, upper abdominal Ultrasound and liverfunction tests are optimum minimal tests for asymptomatic patients.

**References**

1. De.Kernion, J.B.. Ramming, K.P. and Smith. RB. The natural history of metastatic renal cell carcinoma: A computer analysis. J. Urol., 1978;1 20: 148-152.
2. Kradijan, R.M. and Bennington, J.L. Renal carcinoma recurrent 31 years after nephrectomy. Arch. Surg., 1965;90: 192-195.
3. Giuliani,L., Giberti, C., Martorana, G. et al. Radical extensive surgery for renal cell carcinoma: Long term results and prognostic factors. J. Urol., 1990; 143:468-473.
4. Skinner, D.C., Colvin, RB., Vermillion, C.D. et al. Diagnosis and management of renal cell

carcinoma. A clinical and pathological study of 309 cases. Cacer. 1971;28:1165-1177.
5. Hatcher. PA., Anderson. EL., Paulson, D.F. et al. Surgical management and prognosis of renal cell carcinoma invading the vena cava, J. Urol., 1991; 145 :20-23.
6. D. Lanigan, Prognostic factors in renal cell carcinoma. Review article. Br. J. Urol., 1995;75:565-571.
7. Siminovitch, J.M.,Montie, J.E. and Straffon, R,k Prognostic indicators in renal adenocarcinoma, J. Urol., 1983;130:20-23.
8. Bassil, B., Dosoretz, D.E. and Prout, G.R. Validation oftumor, node, metastasis classification of renal cell carcinoma. J. Urol., 1985; 134:450.454.
9. Libertino, J A., Zinman, L. and Watkins, E. Jr: Long term results of resection of renal cancer with extension in inferior vena cava. J. Urol., 1987; 137:21-24.
10. Nurmi. M.J. Prognostic factors in renal carcinoma: An evaluation of operative findings. Br. 3. Urol., 1984;56:270- 275.
11. Middleton, R.J. Surgery for metastatic renal cell carcinoma. J. Urol., 1967;97:973-977.
12. Medeiros, L.J., Gelb, AB. and Weiss, L.M. Renal cell carcinoma: Prognostic significance of morphological parameters in 121 cases. Cancer, 1988;61:1639-1656.
13. Boxer, R.J, Waisman, J., Lieber, MM. or al. Renal carcinoma: Computer analysis of 96 patients treated by nephrectomy. J. UroI., 1979; 122:598-601.
14. Lieber, M., Tomera, F., Taylor, W. et al. Renal adenocarcinoma in young adults: Survival and variables affecting prognosis. J.Urol., 1981; 125:164-168.
15. Mancilla-Jimenez, R., Stanley, R.J. and Blath, R.A. Papillary renal cell carcinoma: A clinical, radiologic and pathologic study of 34 cases. Cancer, 1978; 38:2469-2480.
16. Strochmeyer, T.G. and Salmon, D. J. Proto-oncogenes and tumor suppressor genes in human Urological malighancies.J. Urol., 1994; 151:1.79-197.
17. Horowitz, M., Herr, H.W. and Reuter, V. Untreated hypernephroma of thirty three years. Urology, 1993,41:278-279.
18. Robson, C.J, Churchill, B.M. and Anderson, W. The results of radical nephrectomy for renal cell carcinoma J. Urol., 1969; 101:297-301.