Renal Tumors: The Good, the Bad, and the Ugly

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Abstract- The term renal cell carcinoma (RCC) is used to describe a heterogeneous group of tumors which vary histologically, genetically and molecularly. Recently extensive research has been conducted to identify characteristics which predict outcomes among patients with RCC. In addition to histologic subtype, these include tumor size, patient age, mode of presentation, and various hematologic indices, among others. Several groups have incorporated these clinical and pathologic features into nomograms which help the clinician better define individual patient prognosis and direct the optimum therapeutic approach. In this article we review these prognostic variables and nomograms for RCC.

Keywords: renal, carcinoma, tumor, prognosis, clear cell, papillary, predictor, nomogram

I. Introduction

Renal cancer ranks fourteenth on the list of most common malignancies worldwide.1 Its incidence varies by geographic region, with the highest rates observed in Europe and North America.2 It occurs more commonly in the elderly, with a rising incidence until about 75 years of age.3 Men are affected more commonly than women, although the cancer-specific survival between the groups is similar.4

In the United States, the incidence of renal cancer has continued to increase by approximately 3% each year over the last three decades.5 Although the largest rise has been observed among small tumors, the incidence of large tumors and the overall mortality has continued to increase as well.5 Although a significant downward stage migration has occurred in recent years, up to 30% of patients present with advanced disease at diagnosis.6 In 2008 there were fifty-seven thousand new diagnoses of renal cancer and thirteen thousand deaths, making renal cell carcinoma (RCC) the most lethal of genitourinary cancers.7

RCC is a heterogeneous disease with tremendous variability observed between, and even within, various tumor subtypes. While many tumors behave in a rather indolent manner, others progress rapidly despite even the most aggressive therapies. In recent years an extraordinary amount of research has focused on differentiating the good, bad, and ugly tumors. In this paper we will review various prognostic features that are associated with RCC.

A. Size

Due to the widespread use of abdominal imaging to evaluate symptoms that are often unrelated to the genitourinary tract, the incidental detection of renal masses has become commonplace.8 In fact, it is estimated
that 50% of newly diagnosed renal tumors are discovered in this fashion. Fortunately, this phenomenon has resulted in a downward stage migration and a more favorable prognosis for many patients at diagnosis. Incidentally discovered masses ultimately proven to be RCC tend to be of lower grade and stage, and are associated with an improved 5-year survival rate compared with their symptomatic counterparts.

Several authors have found that the risk of malignancy is directly related to tumor size. Frank et al. reviewed the pathology of over 2,700 patients undergoing surgery for renal tumors between 1970 and 2000, and found that 46% of tumors <1 cm were benign compared to only 6% of tumors >7 cm. For each 1 cm increase in size the odds of malignancy rose by 17%. A recent study from Memorial Sloan-Kettering Cancer Center found that among patients with proven RCC, each 1 cm increase in tumor size increased the odds of having a tumor of high grade by 25%. A nomogram was developed by Lane et al. to predict the likelihood that an enhancing renal mass ≤ 7 cm will be benign based on the age of the patient, size of the lesion on computed tomography (CT), presence or absence of local symptoms, and history of smoking.

Recent data has helped to shed some light on the natural history of the small renal mass. A meta-analysis of 234 solid, untreated, observed renal masses with a mean size of 2.6 cm found that the average growth rate of all lesions was 0.28 cm/year. Among those lesions proven to be RCC by pathological confirmation, the mean growth rate was 0.4 cm/year. Interestingly, lesion size was not predictive of growth rate, and only 1% of patients in this series developed progression to metastatic disease.

Tumor size is one of the most important prognostic indicators among patients with surgically treated renal cell carcinoma. Russo analyzed the survival rates of patients undergoing resection of localized kidney cancers between 1989 and 2004 and found progression-free survival rates of 98%, 95%, 90%, and 70% for patients with tumors <2 cm, 2-4 cm, 4-7 cm, and >7 cm, respectively. Tumor size is an important component of the 2002 TNM staging system for renal cancer, which stratifies organ confined tumors into stage T1 or T2 based on a size cutoff of 7 cm. Although other investigators have proposed different cutoff points for distinguishing T1 from T2 tumors, the is little debate that size remains among the most important prognostic factors. In fact, one study from New Zealand demonstrated that the risk of death increases as a continuous variable with increasing tumor size.

Partial nephrectomy (PN) has become a well-established treatment for RCC, and size has been used to select patients for this modality. Hafez reviewed the Cleveland Clinic experience with PN and found that patients with tumors of size ≤ 4 cm had significantly more favorable 5-year cancer specific survival and recurrence rates than those with tumors greater than 4 cm. Another series of selected patients demonstrated that the outcomes for patients with tumors between 4 and 7 cm were similar whether partial or radical nephrectomy (RN) was performed. Recently a multicenter international series of over fourteen hundred patients also found that there was no difference in the rate of cancer-specific death for patients with stage T1b tumors undergoing partial
versus radical nephrectomy (6% vs. 9%, \( p=0.6 \)).

Other benefits of renal preservation among those undergoing treatment of small renal masses have also become more apparent in recent years. Huang et al. retrospectively reviewed a cohort of 662 patients with normal serum creatinine concentrations and two healthy kidneys who underwent either radical or partial nephrectomy for solitary renal cortical tumors \( \leq 4 \text{ cm} \). Those undergoing RN as compared with PN were 3.8 and 11.8 times more likely to develop chronic kidney disease as defined by glomerular filtration rate (GFR) < 60 and < 45 ml/min per 1.73 m\(^2\), respectively. Chronic kidney disease has been independently associated with death, cardiovascular disease, and hospitalization. Furthermore, another study by Huang found that after a median follow-up of 4 years, patients with tumors < 4 cm who received RN as compared with PN had an almost 40% increased risk of cardiovascular events after surgery and all cause mortality. These data in combination with the excellent oncologic outcomes for partial nephrectomy have led to the development of the American Urological Association Guidelines on the management of clinical stage T1 renal masses.

B. Histology

RCC represents a group of heterogenous tumors with unique histogenic origin, cytogenetic characteristics, and biologic behavior. According to the 1997 American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) classification, there are four major histological subtypes of RCC: clear cell, papillary, chromophobe, and collecting duct carcinomas. The modern concept of origin of renal cancers suggests that clear cell and papillary cancers arise from the proximal tubules, whereas chromophobe tumors, oncocytomas and collecting duct carcinomas arise from the distal convoluted tubules and collecting ducts.

Clear cell RCC is the most common renal cancer subtype, accounting for 60-70% of all cases in the United States. Alterations in chromosome 3p have been detected in the vast majority of sporadic clear cell RCCs, many of which involve the Von Hippel-Lindau (VHL) tumor suppressor gene. Whether clear cell histology portends a worse outcome than other histologic subtypes has been controversial, although there is mounting evidence that clear cell carcinomas are more aggressive. In a recent study from the Mayo Clinic, clear cell carcinoma subtype was an independent predictor of metastasis and cancer specific death as compared to papillary and chromophobe tumors, even after adjusting for other clinicopathologic features.

One newly recognized subset of clear cell RCCs, cystic renal cell carcinoma, deserves mention. Several small series have described the low malignant potential of these tumors and have recommended nephron-sparing surgery whenever feasible. Among a total of 89 patients with cystic renal cell carcinomas across 3 series, only 1 developed a recurrence and none died of renal cancer. Webster et al. recently reviewed the outcomes of 85 patients with this tumor type. The estimated 5-year cancer specific survival for the group was 100%, which was significantly more favorable than
patients with pT1N0 noncystic clear cell RCC. 41

Papillary renal cell carcinoma (PRCC) accounts for 10-15% of RCCs and occurs in two distinct subtypes with quite different prognoses. 37, 42, 43, 44 These two subtypes of papillary RCC (Type I and II) have been described based on differences in histology 44 and molecular and cytogenetic profiles. 45, 46 Type I papillary tumors (genetic basis an abnormality of the MET proto-oncogene with trisomy of chromosome 7) are generally felt to have a better prognosis than clear cell tumors, whereas Type II papillary tumors (most commonly associated with the fumarate hydratase gene) have been associated with higher stage and grade and a worse prognosis than Type I tumors. 46, 47

Chromophobe tumors account for approximately 5% of RCCs. Multiple studies have described a more favorable prognosis for chromophobe than for clear cell tumors. 35, 43, 48, 49 Histologically it is often difficult to differentiate between variants of chromophobe RCC and oncocytoma. Recently, hybrid lesions between oncocytoma and chromophobe RCC have been identified, leading some authors to hypothesize that chromophobe tumors represent a progression from oncocytoma. 50

Collecting duct carcinoma is a rare subtype of RCC with an aggressive clinical course. Fortunately it accounts for less than 1% of all RCCs. Metastases are identified upon presentation in up to two-thirds of patients, and most die within 2 years of diagnosis. 51, 52 Renal medullary carcinoma is another rare but highly aggressive type of RCC. It arises from the renal medulla and occurs almost exclusively in young black males with sickle cell trait or disease. 51 In a series of 6 patients with median age of 24.5 years, the mean time from diagnosis to death was 3 months (range 1-7 months). 53

Translocation tumors are a recently recognized subset of RCCs involving chromosomal translocations of the TFE3 gene on chromosome Xp11. They have distinct histological features consisting of both clear cells and papillary architecture, and tend to occur in young patients. Translocation tumors occurring in adults tend to be highly aggressive, often present with widely metastatic disease, and carry a poor prognosis. Interestingly, affected children who present with nodal but not systemic metastases seem to have a more favorable outcome than anticipated. Thus, it appears that TFE3 translocation tumors occurring in children behave in a more indolent fashion than in adults. Larger series with more patients are needed to further characterize the clinical course of these rare tumors. 54

C. Grade and Other Histologic Features

The Fuhrman system is the most commonly used grading scheme for RCC. It distinguishes grades 1 to 4 based on nuclear size and morphology and as well as nucleolar prominence. 50 Nuclear grade has been shown to correlate with tumor size, stage, and the presence of metastasis. 48, 51 Although the prognostic value of the Fuhrman grading system for papillary and chromophobe tumors has been debated, 32, 55-57 its independent predictive value for clear cell tumors has been demonstrated in multiple studies. 32, 58, 59 In a nationwide study of over six hundred patients from Iceland, nuclear grade was an independent predictor of
survival among patients with pathologically confirmed RCC.\textsuperscript{32, 58}

One of the main difficulties in assigning nuclear grade has been poor inter-
observer reproducibility.\textsuperscript{51, 60, 61}

Several other histologic features have demonstrated prognostic importance. Sarcomatoid RCC, initially considered a distinct subtype, is now recognized as a high-grade transformation that can arise in any subtype of RCC.\textsuperscript{62} This rare growth pattern, which is present in less than 5% of RCC cases, is characterized by spindled elements and automatically classifies the tumor as nuclear grade 4.\textsuperscript{48} One study compared 101 patients with sarcomatoid differentiation to a cohort of 851 lacking this pathologic feature. Those with sarcomatoid change presented at a higher stage and had a worse prognosis. The 5-year disease specific survival of those with and without sarcomatoid change was 22% and 79%, respectively.\textsuperscript{62}

Tumor necrosis is another histological feature that affects prognosis. Lam reviewed 310 patients with localized and metastatic RCC and found that the presence and extent of histologic necrosis was an independent predictor of survival among those with localized disease.\textsuperscript{63} Another important study from the Mayo Clinic examined the importance of tumor necrosis among various histologic RCC subtypes. They found that tumor necrosis was present in 28% of clear, 47% of papillary, and 20% of chromophobe RCCs. Even after adjusting for tumor stage, size, and grade, the presence of necrosis was associated with a 4 to 5 fold increased risk of death among patients with clear cell and chromophobe but not papillary RCC.\textsuperscript{64}

D. Age

The incidence of renal cell carcinoma increases with age, and only 5% of tumors occur in patients younger than 40 years. Several studies have found that younger patients with pathologically-proven RCC have a better prognosis than older patients, which may be related to a lower grade and stage at diagnosis. Eggener et al. performed a multi-
institutional review of all patients under the age of 45 undergoing surgical resection of a solid or complex cystic renal mass. 56% presented with symptoms and 7% had a family history of VHL. Overall, 20% of lesions were benign, and young females were much more likely than males to have benign pathology (36% vs. 9%, \textit{p}<0.01). Among the 80% of malignant lesions, almost all of which were RCC, 76% were grade \leq 2 and 89% were organ-confined. Despite a symptomatic presentation, younger patients with RCC appeared to have a more favorable prognosis.\textsuperscript{65} Siemer and colleagues also noted a higher incidence of benign tumors (40%) in women under the age of 40.\textsuperscript{66}

In a study of over one thousand patients which included 70 “young patients” (defined as age under 45), young patients were more likely to have lower stage and grade tumors and had a higher 5-year cancer-specific survival than older patients.\textsuperscript{67} Jung also found that young age was associated with lower grade and stage and was an independent predictor of survival among patients with low stage clear cell RCC.\textsuperscript{68} Interestingly, another study from the Memorial Sloan Kettering Cancer Center found that despite more unfavorable histopathological characteristics and a higher incidence of lymph node metastases, younger patients had an improved disease-specific and
recurrence-free survival on multivariable analysis.  

Mode of Presentation

Despite the increase in incidentally discovered renal tumors as previously mentioned, a significant proportion of patients still present symptomatically with flank pain, an abdominal mass, hematuria, or with constitutional symptoms. Investigators from the University of Michigan found in a 2002 study that 57% of RCCs were incidentally discovered while 42% were found upon workup of tumor-related symptoms. A symptomatic presentation correlated with aggressive histology, advanced disease, and in multivariate analysis was a predictor of worse disease-free and disease-specific survival. Patard et al. from France have also created a symptom based classification, termed the S classification, which stratifies patients into 3 groups based on the presence or absence of symptoms. Patients who are asymptomatic are classified as S1, those with local symptoms as S2, and those with systemic symptoms as S3. They found S classification, in addition to TNM stage and Fuhrman grade, to be an independent prognostic factor among 388 patients with renal tumors. These findings were replicated in a multi-institutional study of over 2,200 patients, where the risk of death from RCC was 2.8 and 8.8 times higher among patients with local and systemic symptoms, respectively, when compared to those who were asymptomatic.

In contrast, other studies examining the mode of presentation suggest that incidentally discovered tumors may be of lower stage and grade than symptomatic ones, but the mere presence or absence of symptoms may not be an independent predictor of prognosis. Thus, the significance of various presenting symptoms has been examined in more detail. Kim performed a multivariable analysis which included grade, stage, and Eastern Cooperative Oncology Group performance status (ECOG PS) on a group of over one thousand patients with RCC and found that 4 findings, namely hypoalbuminemia, weight loss, anorexia, and malaise, were independent predictors of disease specific survival. These specific symptoms were termed “cachexia related findings,” and the presence of just one was associated with a worse disease specific survival in patients with both localized and metastatic RCC.

A closely related variable which has also shown tremendous importance in the prognosis of patients with RCC is performance status (PS)). The two most commonly used scales are the Karnofsky and ECOG PS, both of which attempt to quanitate the overall impact of the disease on the health of the patient by evaluating their ambulatory status. Multiple studies have confirmed the independent impact of PS on survival in patients with both metastatic and localized renal cell carcinoma.

Hematologic Indices

Several different hematologic indices have demonstrated prognostic significance in patients with RCC. A complete blood count (CBC), which is inexpensive and routinely obtained in
patients with renal tumors, may help to predict outcomes of patients with both metastatic and localized RCC. A recent multi-institutional study evaluated whether thrombocytosis and anemia could improve the accuracy of already well-established predictors of RCC survival. In a cohort of over eighteen hundred patients, both of these factors were significant predictors of cancer-specific survival in both univariable and multivariable analysis. However, when added to other established predictors, including TNM stage, grade, ECOG-PS and histologic subtype, the ability to predict RCC-specific survival was not improved. Thus, the importance of these laboratory values in clinical practice is yet to be determined.

Renal cell carcinoma is a tumor known to have complex interactions with the immune system, and markers of a systemic inflammatory response have been shown to correlate with disease progression and survival. The best studied inflammatory marker, c-reactive protein (CRP), is an acute phase reactant produced by the liver in response to upregulated levels of interleukin-6 produced by the tumor. Recently Johnson et al. demonstrated that the absolute preoperative CRP level was an independent predictor of relapse-free and overall survival in the first year among patients undergoing surgery for clinically localized T1-T3 RCC. The same group later reported that postoperative CRP levels may be an even better predictor of metastasis and death in this same group of patients. In addition, Saito et al. found that following CRP kinetics during the postoperative period may help to predict survival. Those with normal preoperative levels of CRP experienced the best survival and those with preoperatively elevated levels that normalized after surgery fared better.
than those whose CRP remained elevated. The predictive value of CRP levels in patients undergoing surgery with curative intent as well as in patients with metastatic disease has been demonstrated by other groups.

Several newer indices have been the subject of recent investigation. Erythrocyte polyamines are important structures involved in DNA synthesis and stabilization as well as cell proliferation. Preoperative circulating levels of two polyamines, spermine and spermidine, were recently found to be independent predictors of cancer specific mortality in a group of 399 patients treated with radical or partial nephrectomy. Furthermore, when added to TNM stage, Fuhrman grade, and symptom classification, the predictive accuracy was improved. Other serum markers including VEGF, interleukin-6, and carbonic anhydrase IX have shown promise, but all of these require further study before they are routinely used in clinical practice.

Prognostic Models for RCC

As mentioned previously, the umbrella of renal cell carcinoma represents an extremely heterogeneous group of tumors. Obviously no single factor can account for the wide variability in outcomes observed in individual patients. Therefore, multiple prognostic models (nonograms) have been developed which take into account many of the clinical and pathologic factors discussed in the previous sections. These nomograms are user-friendly and provide the clinician and patient with the probability of a specific outcome over time, representing an advantage over multivariable models which provide more abstract data that are not immediately applicable in the clinical setting. Therefore, these algorithms may be used by practitioners to guide decisions regarding surgery, surveillance, and adjuvant therapy, as well as for the inclusion of patients in clinical trials. The most commonly used nomograms are listed in Table 1.

Preoperative Models

Several groups have developed nomograms which use preoperative variables to help predict the development of disease recurrence following resection in nonmetastatic RCC patients. Raj and associates pooled data from over 2,500 patients with renal masses localized to the kidney who were treated surgically at the Mayo Clinic and Memorial Sloan-Kettering Cancer Center. They found that the size of the mass, evidence of lymphadenopathy, necrosis on imaging, and mode of presentation were predictors of eventual metastasis. They constructed a nomogram incorporating these factors to predict the 12 year likelihood of disease recurrence.

Currently most patients with renal masses undergo surgical treatment, from which pathologic data is obtained. Lane and Kattan point out that unfortunately, none of these preoperative algorithms perform as well as those which incorporate pathologic information. In a study comparing the predictive accuracy of four prognostic models, those including pathologic data were more accurate than those which included only preoperative data. However, as minimally invasive treatments and active surveillance become more popular for patients with RCC, nomograms based on clinical information alone will assume a more important role.

Postoperative Models
Numerous models have been developed to predict clinical outcomes based on clinical and pathologic data. The most widely used are the Kattan postoperative nomogram,\textsuperscript{113,76} the UISS (UCLA Integrated Staging System),\textsuperscript{76} the SSIGN score (tumor Stage, tumor Size, nuclear Grade and presence of Necrosis),\textsuperscript{114} and the Karakiewicz postoperative nomogram.\textsuperscript{115}

Kattan et al. from the Memorial Sloan-Kettering Cancer Center developed a nomogram to predict the 5-year progression-free survival of patients undergoing radical nephrectomy for non-metastatic RCC of various histologic subtypes. The four factors included in this nomogram were the presence of symptoms, histologic subtype, tumor size, and standard TNM stage according to the 1997 version.\textsuperscript{113} The observation that over 90% of patients who develop metastases after surgery for a clinically localized primary tumor have clear cell histology led the group to later develop a modified nomogram limited to patients with clear cell histology (Figure 1).\textsuperscript{116} When applied to external populations in Europe, the original Kattan nomogram has demonstrated variable prognostic accuracy ranging from 61-81%.\textsuperscript{112,117}

In 2002 Zisman et al. published the UCLA Integrated Staging System (UISS) to determine the prognosis of patients undergoing radical or partial nephrectomy for localized and metastatic RCC in terms of overall survival. The UISS uses stage, grade, and ECOG PS to stratify patients into five groups, with the 5-year survival of groups I-V being 94%, 67%, 39%, 23%, and 0%, respectively.\textsuperscript{76} The UCLA group subsequently modified the UISS into an outcome algorithm to stratify patients into low, intermediate, and high risk groups based on the same set of variables (Figures 2a and 2b).\textsuperscript{118} This modified system has been validated in several external patient groups, including a cohort of over four thousand patients from 8 international centers where the predictive accuracy was found to be 81%.\textsuperscript{77,119,77}

The group from the Mayo Clinic developed an outcome prediction model for patients with clear cell RCC treated by radical nephrectomy. In their series of 1801 patients, four factors, 1997 TNM stage, tumor size >5 cm, nuclear grade, and tumor necrosis were all associated with death from RCC on multivariable analysis. The investigators thus created the SSIGN scoring algorithm (with scores ranging from 0-10) based on these four factors to predict cancer specific survival rates at 1, 3, 5, 7, and 10 years (Tables 2a and 2b). For example, the 5-year disease specific survival rate of patients with a SSIGN score of 0-1 was 99%, compared with 7% for those with a score of 10.\textsuperscript{114} European and Japanese studies have subsequently confirmed the prognostic accuracy of the SSIGN algorithm.\textsuperscript{120-122}

Finally, in 2007 Karakiewicz et al. attempted to improve upon the accuracy of the above mentioned models discussed above by including more variables which have traditionally been shown to predict survival among patients with RCC. The cohort upon which the model was developed included over 2500 patients with various stages of RCC treated at five different centers. Their final model ultimately incorporated TNM stage, tumor size, histologic subtype, age, sex, and symptoms at presentation in order to predict, 1, 2, 5, and 10-year cancer specific mortality (Figure 3). The internally validated accuracy of the nomogram was 86%. In the same study
an external validation of this nomogram yielded a predictive accuracy of about 88%, which was better than that of the UISS when tested on the same group of patients. 115

Models for Metastatic RCC

Several models have been developed to predict survival in patients with metastatic RCC. In 2002 Motzer et al. developed the Memorial Sloan-Kettering Cancer Center prognostic classification which stratifies patients into good, intermediate, and poor prognosis groups based on the number of adverse factors present. These adverse factors include Karnofsky index <80%, LDH >1.5 times normal, hemoglobin < than 13 if male or 11.5 if female, corrected calcium >10, and interval between RCC diagnosis and beginning of systemic treatment < 1 year. The median survival was 30 months for the good risk patient group (0 factor present), 14 months for intermediate risk group (1-2 factors present), and 5 months for the poor risk group (>2 factors present). This is the most widely used model by practicing physicians for counseling patients with metastatic RCC and for determining inclusion in clinical trials. 123

Summary

It has become increasingly clear in recent years that renal cancer is not one disease but rather a heterogeneous family of different tumor types that vary histologically, genetically and molecularly. This variability has been underscored by the fact that these tumor subtypes may respond quite differently to various systemic therapies used for the treatment of renal cancer. In addition to tumor subtype, other variables (including stage, grade, patient age, tumor size and many others) have been shown to affect prognosis, even within an individual subtype of renal cancer. It is therefore critical that healthcare professionals who treat these tumors become familiar with the impact that tumor subtype and other variables may have in predicting the outcomes and response to therapy of their individual patients. In doing so, healthcare providers should understand and employ the various prognostic nomograms that may be used to better define individual patient prognosis and direct the optimum therapeutic approach to their patients.

FIGURE LEGENDS
Figure 1 Legend: Nomogram predicting the probability of freedom from recurrence after nephrectomy for clear cell RCC. Instructions for use: Locate the tumor size on the size axis. Draw a line upwards to the Points axis to determine how many points the patient receives for the tumor size. Repeat this process for the other axes, each time drawing a line straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total points axis. Draw a straight line down to find the probability that the patient will remain free of recurrence for 5 years. (Reproduced from Sorbellini et al. J Urol 2005;731(1):50 with permission)

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5-yr. Predicted Probability of Freedom from Recurrence:
- 0.99
- 0.865
- 0.96
- 0.850
- 0.9
- 0.78
- 0.605
- 0.40
- 0.30
- 0.20
- 0.10
- 0.01

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**A. Nonmetastatic Cases**

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Figure 2a Legend: Decision box A assigns N0M0 nephrectomized patients in to risk groups. Progress from top to bottom using the 1977 AJCC stage, grade, and ECOG PS. Decision box B assigns N+/M+ patients. (Reproduced from Zisman et al. J Clin Oncol 2002;20:4559 with permission)
Figure 2b Legend: Disease-specific survival divided into N0M0 and N+/M+ patients and into the corresponding risk groups. LR= low risk, IM= intermediate risk, and HR= high risk. (Reproduced from Zisman et al. J Clin Oncol 2002;20:4559 with permission)

Figure 3 Legend: Karakiewicz nomogram predicting renal cell carcinoma (RCC)-specific survival at 1, 2, 5, and 10 years. (Reproduced from Karakiewicz et al. J Clin Oncol 2007;25:1316 with permission)
### TABLES

#### Preoperative Models
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- Raj Preoperative Nomogram \(^{108}\)

#### Postoperative Models
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- MSKCC Prognostic Classification \(^{123}\)

Table 1. Commonly Used Nomograms in RCC

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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Necrosis:</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2a. The SSIGN scoring algorithm. The scores from each category in this table are added together and the total is used to determine survival according to Table 2b. (Data from Frank et al. J Urol 2005;173:48-51 with permission)

<table>
<thead>
<tr>
<th>SSIGN Score</th>
<th>% Estimated Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year</td>
</tr>
<tr>
<td>0-1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>99.1</td>
</tr>
<tr>
<td>3</td>
<td>97.4</td>
</tr>
<tr>
<td>4</td>
<td>95.4</td>
</tr>
<tr>
<td>5</td>
<td>91.1</td>
</tr>
<tr>
<td>6</td>
<td>87.0</td>
</tr>
<tr>
<td>7</td>
<td>80.3</td>
</tr>
<tr>
<td>8</td>
<td>65.1</td>
</tr>
<tr>
<td>9</td>
<td>60.5</td>
</tr>
<tr>
<td>≥ 10</td>
<td>36.2</td>
</tr>
</tbody>
</table>

Table 2b. Estimated cancer specific survival following radical nephrectomy for clear cell RCC by SSIGN Score (Data from Frank et al. J Urol 2005;173:48-51 with permission)

### ABBREVIATIONS USED

AJCC = American Joint Committee on Cancer  
CBC = complete blood count  
CT = computed tomography  
CRP = c-reactive protein  
ECOG = Eastern Cooperative Oncology Group  
ESR = erythrocyte sedimentation rate  
MET = hepatocyte growth factor receptor  
PN = partial nephrectomy  
PRCC = papillary renal cell carcinoma  
PS = performance status  
RCC = renal cell carcinoma  
RN = radical nephrectomy  
TFE3 = transcription factor E3
UICC = International Union Against Cancer
VEGF = vascular endothelial growth factor

REFERENCES


27. Patard JJ, Shvarts O, Lam JS, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on


41. Webster WS, Thompson RH, Cheville JC, Lohse CM, Blute ML, Leibovich BC. Surgical resection provides excellent outcomes for patients


57. Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Fuhrman grading is


86. Kawai Y, Matsuyama H, Korenaga Y, et al. Preoperative erythrocyte sedimentation rate is an independent


98. Fujikawa K, Matsui Y, Oka H, Fukuzawa S, Takeuchi H. Serum C-


