

# Staging of renal cell carcinoma: Current concepts

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## ABSTRACT

The most important and widely utilized system for providing prognostic information following surgical management for renal cell carcinoma (RCC) is currently the tumor, nodes, and metastasis (TNM) staging system. An accurate and clinically useful staging system is an essential tool used to provide patients with counseling regarding prognosis, select treatment modalities, and determining eligibility for clinical trials. Data published over the last few years has led to significant controversies as to whether further revisions are needed and whether improvements can be made with the introduction of new, more accurate predictive prognostic factors. Staging systems have also evolved with an increase in the understanding of RCC tumor biology. Molecular tumor biomarkers are expected to revolutionize the staging of RCC by providing more effective prognostic ability over traditional clinical variables alone. This review will examine the components of the TNM staging system, current staging modalities including comprehensive integrated staging systems, and predictive nomograms, and introduce the concept of molecular staging for RCC.

**Key words:** Kidney cancer, molecular markers, nomograms, prognosis, staging

## INTRODUCTION

Over 200,000 new cases of kidney cancer are diagnosed and more than 100,000 deaths occur from this disease each year globally.<sup>[1]</sup> Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies and is steadily increasing at a rate of about 2.5% per year across population groups with the greatest increase observed in the incidence of localized tumors.<sup>[2-4]</sup> RCC is a highly aggressive tumor and the most lethal of urologic malignancies.<sup>[5]</sup> Approximately one-third of patients present with metastatic disease and up to 40% of patients will recur following surgery for clinically localized disease.<sup>[6]</sup> Significant advances in the diagnosis, staging, and treatment of patients with RCC have resulted in improved survival of a select group of patients and an overall change in the natural history of the disease.<sup>[3,7,8]</sup>

## TUMOR, NODE, AND METASTASIS (TNM) STAGING SYSTEM

Anatomical criteria have traditionally been used to stage RCC. Flocks and Kadesky<sup>[9]</sup> were the first to

propose a formal staging system that stratified patients according to tumor involvement based on physical tumor characteristics and the location of tumor spread. Robson, *et al.*<sup>[10]</sup> later modified these criteria to include vascular involvement and reported an overall 52% 5-year survival and a 66% 5-year survival in patients with localized disease. This study drew attention to the basic surgical principles for the successful management of renal tumors and the importance of stratifying the anatomic spread of the tumor for the purpose of patient prognostication. These basic principles included early ligation of the renal vessels to minimize risk of vascular tumor emboli, resection of Gerota's fascia including the kidney and adrenal gland, and extensive lymphadenectomy including the para-aortic and paracaval nodes from the crus of the diaphragm to the bifurcation of the aorta. Similarly, the tumor, nodes, and metastasis (TNM) system proposed by the Union Internationale Contre le Cancer (UICC) systematically assesses local tumor growth, lymph node involvement, and distant metastasis to categorize patients.<sup>[11]</sup>

The primary size of the tumor is a key component of the TNM staging system and remains one of the most important prognostic factors for RCC.<sup>[7,8]</sup> In 1997, the cut-off size for the T1 stage was expanded from 2.5 to 7 cm, which has led to controversy.<sup>[12,13]</sup> The increasing widespread and now mainstream use of a partial nephrectomy for smaller tumors has also made the T1 cutoff criteria not only important in terms of prognostic value, but also in relation to eligibility

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for this surgery. Hafez, *et al.*<sup>[14]</sup> attempted to delineate the optimal cutoff size for tumors amenable to a partial nephrectomy. Patients with T1 tumors 4 cm or smaller who underwent a partial nephrectomy had a significantly better survival rate when compared with those who had larger tumors. Over the past decade, evidence from other major clinical series has shown the effectiveness and safety of partial nephrectomies in the treatment of renal tumors 4 cm or smaller.<sup>[15-19]</sup> As a result, the 2002 TNM T1 category was amended to T1a and T1b based on a 4 cm cutoff.<sup>[20]</sup> Although an elective partial nephrectomy is generally performed in patients with a tumor smaller than 4 cm, there is emerging data that it can be performed on patients with larger tumors that are anatomically amenable, provided an adequate surgical margin can be safely obtained.<sup>[21,22]</sup>

Several investigators have attempted to further improve the prognostic accuracy of T2 tumors by stratifying based on size. Frank, *et al.*<sup>[23]</sup> found that tumors larger than 10 cm behaved more aggressively compared with those between 7 and 10 cm after adjusting for regional lymph node involvement and distant metastases. In an international multicenter study, Klatte, *et al.*<sup>[24]</sup> reported that tumors larger than 11 cm were associated with the presence of metastatic disease compared with those between 7 and 11 cm. Stratification by a tumor size cut-off of 11 cm demonstrated a 5- and 10-year survival of 73% and 65% for T2 tumors 11 cm or smaller and 57% and 49% for tumors greater than 11 cm, respectively. Tumor size was retained as an independent prognostic factor for survival and was the strongest prognostic factor for patients with non-metastatic T2 disease.

A 5-year cancer-specific survival rate for T3 disease ranges from 37% to 67%, which reflects this broad category that includes various clinical situations that involve tumor extension beyond the renal capsule.<sup>[25,26]</sup> Tumors that extend into the perirenal fat but not beyond Gerota's fascia or have direct adrenal involvement are currently classified as T3a. The impact of fat invasion on the prognosis of patients with RCC is well documented. However, different locations of fat invasion have been reported to portend different prognoses. Thompson, *et al.*<sup>[27]</sup> reported that patients with renal sinus fat invasion were 1.6 times more likely to die of RCC compared with those with peripheral perinephric fat invasion. Furthermore, the risk of death persisted in multivariate analysis after adjusting for regional lymph node involvement and the presence of distant metastases. In contrast, Margulis, *et al.*<sup>[28]</sup> reported no difference in the 5-year cancer-specific survival rate between patients with sinus fat invasion and those with perinephric fat invasion only. In addition, neither sinus fat invasion nor the location of extrarenal extension correlated with the cancer-specific survival rate following surgical treatment. The presence of renal fat involvement appears to increase the risk of death from RCC among patients with venous tumor thrombus.<sup>[29-31]</sup> Leibovich, *et al.*<sup>[29]</sup> reported that among patients with

T3b disease, those with concomitant perinephric or sinus fat invasion were 1.87 times more likely to die of RCC compared with patients without fat invasion. Klatte, *et al.*<sup>[30]</sup> reported that concomitant perinephric fat invasion among patients with T3b and T3c disease was an independent prognostic factor and that redefinition of the T3 classification with the incorporation of fat invasion improved prognostic accuracy.

The role of tumor size in T3a tumors has attracted little attention in literature. Siemer, *et al.*<sup>[32]</sup> analyzed patients with perinephric fat invasion and identified an ideal tumor size cut-off of 7 cm. Patients with T3a tumors 7 cm or smaller yielded similar survival to patients with T1 tumors and patients with T3a tumors larger than 7 cm yielded similar survival to T2 tumors. The current T1-2 and T3a classification for RCC has been debated in other studies. Murphy, *et al.*<sup>[33]</sup> reported worse outcomes for patients with T2 disease compared with those patients with T3a disease suggesting that tumor size was a stronger prognostic factor than tumor invasion through the renal capsule. Gilbert, *et al.*<sup>[34]</sup> also reported similar outcomes between patients with T1-2 and T3a disease. Siddiqui, *et al.*<sup>[35]</sup> investigated the association of perinephric and sinus fat invasion with death from RCC independent of tumor size. Patients with fat invasion and tumors 4 cm or smaller, 4 to 7 cm, and larger than 7 cm were 6.15, 4.13, and 2.12 times, respectively more likely to die from RCC compared with those without fat invasion. Lam, *et al.*<sup>[36]</sup> reported no difference in the cancer-specific survival rate between patients with T2 and T3a tumors 7 cm or smaller, but both groups were superior to patients with T3a tumors larger than 7 cm. Furthermore, patients with T3a tumors larger than 7 cm had a 1.36-fold increased risk of death from RCC compared with patients with T3a tumors 7 cm or smaller and T2 tumors. In addition, patients with T3a tumors larger than 7 cm had the same prognosis as patients with T3b tumors.

A few patients presented with RCC involving the ipsilateral adrenal gland at the time of diagnosis.<sup>[37,38]</sup> The current TNM staging system also categorizes patients with adrenal involvement into the T3a group. Recent reports have shown that patients with direct extension into the adrenal gland fair worse than those with extension into perirenal fat only.<sup>[39,40]</sup> Han, *et al.*<sup>[39]</sup> reported that patients with adrenal involvement fared worse than those with perinephric fat invasion and no adrenal involvement. Furthermore, the survival of patients with T3a disease and adrenal involvement was not better than patients with T4 tumors. Although a correlation existed between adrenal invasion and higher tumor grade and lymph node involvement and metastatic disease, adrenal invasion was found to be an independent predictor of poor prognosis. In addition, it has been shown that stage for stage patients with direct adrenal invasion fair worse than those without.<sup>[41]</sup> Others have corroborated the above findings concluding that tumors with adrenal involvement from direct extension appear

to have a similar outcome to patients with T4 disease.<sup>[40,42]</sup> Several studies have suggested that removal of the ipsilateral adrenal gland is not routinely necessary during a radical nephrectomy.<sup>[37,43,44]</sup> Current evidence suggests that the rate of adrenal metastasis is low and that modern day imaging modalities are sensitive enough to pick up adrenal lesions.<sup>[38,44]</sup> Given the small percentage of patients with adrenal involvement and the use of detailed preoperative imaging, the vast majority of those with RCC can be spared the potential morbidity associated with an ipsilateral adrenalectomy.

RCC invades the venous system in 4–9% of newly diagnosed patients.<sup>[45,46]</sup> In 1997, inferior vena cava (IVC) tumor thrombus located above the diaphragm, previously stage T4, was changed to T3c and thrombus involvement below the diaphragm, previously staged T3c, was changed to T3b with renal vein (RV) involvement.<sup>[11]</sup> Most studies have found no difference in survival based on the level of IVC involvement<sup>[47,48]</sup> or based on the involvement of RV versus IVC.<sup>[48,49]</sup> However, it has been suggested recently that long-term survival may be better in patients with RV involvement compared with IVC involvement.<sup>[50]</sup> Recent studies have demonstrated a 5-year survival to range from 47% to 69% for patients with venous involvement and a tumor limited to the kidney.<sup>[51–55]</sup> With modern advances in surgical technique, a surgical resection can be performed with acceptable morbidity.<sup>[54,55]</sup> In select patients with metastatic disease, resection of the tumor thrombus followed by immunotherapy has been recommended.<sup>[55,56]</sup>

The overall risk of lymph node metastasis is approximately 20% and 5-year survival rates of patients with lymph node involvement ranges from 11–35%.<sup>[57–59]</sup> However, the risk of lymph node involvement varies depending on primary tumor stage and size, vascular involvement, presence of metastases, and extent of lymphadenectomy performed.<sup>[57,60]</sup> Patients with clinically localized disease have a relatively low incidence (2–9%) of nodal involvement,<sup>[60]</sup> whereas patients with metastatic disease or vascular involvement have an incidence as high as 45%.<sup>[57]</sup> In a review of 900 patients, positive lymph node status was associated with larger, higher grade, more locally advanced tumors more likely to demonstrate sarcomatoid features and were 3 to 4 times more likely to have distant metastatic disease.<sup>[57]</sup> Furthermore, patients with metastatic RCC and concomitant lymph node involvement demonstrated a significantly worse outcome compared with patients with metastatic disease alone. Patients with nodal disease manifested poorer response rates to immunotherapy.<sup>[58]</sup> However, patients with node-positive disease who underwent a lymphadenectomy had better responses to immunotherapy and higher survival rates compared with patients whose involved lymph nodes were left in place.<sup>[58]</sup> Vasselli, *et al.*<sup>[59]</sup> also reported that patients without preoperative evidence of lymph node involvement had a significantly longer survival rate than

those with lymph node involvement.

Although it has been specified since the 6th edition of the TNM classification that histological examination of a regional lymphadenectomy specimens should routinely include 8 or more lymph nodes, few studies have challenged the N1-N2 subclassification. Previous studies have focused on the number of lymph nodes that were required for accurate staging as well as the utility and extent of the lymphadenectomy.<sup>[61]</sup> Terrone, *et al.*<sup>[62]</sup> reported no survival difference between N1 and N2 tumors in patients with locally advanced or metastatic disease. Among patients with positive lymph nodes, the two relevant prognostic cut-offs were 4 involved nodes and a 60% lymph node density cut-off. In addition, lymph node density was retained as an independent prognostic variable. Canfield, *et al.*<sup>[63]</sup> analyzed the prognostic significance of nodal disease in the absence of distant metastatic disease. The median survival rate in patients with N2 disease was significantly worse compared with patients with N1 disease. In addition, more than 1 positive node was an independent predictor of decreased disease-free and overall survival. Dimashkieh, *et al.*<sup>[64]</sup> examined the associations of pathological features of lymph node metastases with outcome in a cohort of patients treated with radical nephrectomy for unilateral, sporadic M0 RCC. There was no significant difference in the survival rate between patients with N1 and N2 disease. However, patients with extranodal extension were twice as likely to die of RCC compared with patients in whom metastases did not extend outside of the lymph node capsule.

## COMPREHENSIVE INTEGRATED STAGING SYSTEMS AND PREDICTIVE NOMOGRAMS

The anatomical, histological, and clinical factors that influence disease recurrence and survival in RCC make counseling patients particularly challenging. Many centers have aimed to integrate these independent prognostic indicators into comprehensive outcome models for both non metastatic and metastatic RCC to assist clinicians in facilitating patient counseling and identifying those patients who might benefit from treatment. The first report addressing this issue appeared in 1986 in which the factors predicting outcome for patients with metastatic RCC included performance status (PS), presence of pulmonary metastases, and metastatic-free interval.<sup>[65]</sup> More recently, several groups have created similar models designed to include patients with localized and metastatic disease.

Elson, *et al.*<sup>[66]</sup> presented an analysis of 610 patients with recurrent or metastatic RCC who had been treated with chemotherapy in clinical trials sponsored by the Eastern Cooperative Oncology Group (ECOG). A scoring system was developed to stratify patients into 5 categories based on PS (0 to 1 vs. 2 to 3), time from initial diagnosis (>1 year vs. 1 year), number of metastatic sites, prior cytotoxic chemotherapy,

and recent weight loss. The Karnofsky or ECOG-PS scales are a convenient common denominator for the overall impact of multiple objective and subjective symptoms and signs on patients. Using this system, median survival times ranging from 2.1 to 12.8 months were observed across the five separate categories. As this cohort was examined prior to the initiation of immunotherapy, its validity for today's patient population is questionable.

Motzer, *et al.*<sup>[67]</sup> developed a model based on 670 patients with advanced RCC treated in 24 separate clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC) including 394 patients treated with IFN- $\alpha$  or IL-2. This model was created by defining the relationship of pretreatment clinical features and survival, which included the following risk factors: low Karnofsky PS score, high serum lactate dehydrogenase levels, low hemoglobin levels, hypercalcemia, and prior nephrectomy. The median survival rate was 10 months and significantly shorter survival occurred in patients with poor PS (Karnofsky scale <80%), high lactate dehydrogenase (>1.5 times the upper limit of normal), low hemoglobin, high-corrected calcium (>10 mg/dL), and absence of prior nephrectomy. Patients were stratified into favorable-, intermediate-, and poor- risk groups according to the number of risk factors present. Patients at poor risk with 3 or more risk factors had a median survival of 4 months, whereas median survival improved to 20 months in those with no risk factors.

To analyze prognostic factors that would benefit modern day clinical trials, Motzer, *et al.*<sup>[68]</sup> reviewed 137 patients with metastatic RCC enrolled in clinical trials at MSKCC from 1990 onwards. The median overall survival rate for this group was 12.7 months. Independent predictors of worse survival rates were poor PS (Karnofsky scale <80%), low hemoglobin levels (less than or equal to 13 g/dL in males and 11.5 g/dL in females), and elevated corrected serum calcium ( $\geq 10$  mg/dL). The number of poor prognostic variables stratified patients into favorable-risk (no risk factors), intermediate-risk (one risk factor), and poor-risk (two or three risk factors) groups. The favorable-, intermediate-, and poor-risk groups demonstrated overall 1- and 3-year survival rates of 76% and 25%, 49% and 11%, and 11% and 0%, respectively.

A study of 353 patients with previously untreated advanced RCC at the Cleveland Clinic was conducted to assess and validate the model proposed from MSKCC.<sup>[69]</sup> Four of five prognostic factors (time from diagnosis to entry into the study, serum lactate dehydrogenase, corrected serum calcium, and hemoglobin) identified by the MSKCC group were independent predictors of survival. In addition, prior radiotherapy and the presence of hepatic, lung, and retroperitoneal nodal metastases were found to be independent prognostic factors. Using the number of metastatic sites as surrogates for individual sites (none

or one vs. two or three sites), the MSKCC definitions of risk groups were expanded to accommodate these two additional prognostic factors. Using this expanded criteria, favorable-risk was defined as zero or one poor prognostic factor, intermediate-risk was defined as two poor prognostic factors, and poor-risk was defined as more than two poor prognostic factors.

The International Kidney Cancer Working Group is currently establishing a comprehensive database from centers that treat patients with metastatic RCC. This will be used to develop a set of prognostic factors in patients with metastatic RCC and ultimately to derive a single validated model. Preliminary studies were performed to determine the availability of a database that could be used for the planned analysis of prognostic factors, which involved the examination of 782 patients treated by the Groupe Francais d'Immunotherapie<sup>[70]</sup> and patients treated at the Cleveland Clinic.<sup>[69]</sup> These two groups were similar in their distribution of various clinical factors and survival.<sup>[71]</sup> These findings suggest that the use of an international database would be a reasonable approach to identify prognostic factors and validate a model for patients with this disease. Additionally, this database could serve as a resource to study the natural history of this illness and aid in the design and analysis of clinical trials for patients with metastatic RCC.

The Kattan postoperative prognostic nomogram<sup>[72]</sup> was created to predict the probability of tumor recurrence within 5 years in patients undergoing a radical nephrectomy for RCC. The nomogram assigns numerical scores to various prognostic indicators that include presence of symptoms, histology, tumor size, and TNM staging criteria. In a study of 601 patients with RCC who were treated with a nephrectomy, the nomogram appeared accurate and discriminating with an area under the receiver operating curve of 0.74. This nomogram was later modified to exclude histologic subtype and the analysis was limited to clear cell RCC.<sup>[73]</sup> The 5-year probability of freedom from recurrence for the patient cohort was 80.9%. This nomogram has a concordance index of 0.82 and external validation revealed it to be accurate and discriminating.

The UCLA integrated staging system (UISS) is an extensive prognostic system that has been created for both localized and metastatic RCC.<sup>[74]</sup> The initial UISS contained 5 groups based on TNM stage, Fuhrman grade, and ECOG-PS all found to be independent predictors of survival. Projected 2-year survival rates and 5-year survival rates for patients in UISS Groups I through V were 96% and 94%, 89% and 67%, 66% and 39%, 42% and 23%, and 9% and 0%, respectively. The UISS was internally validated using a bootstrapping technique and an expanded database of patients treated at UCLA between 1989 and 2000,<sup>[75]</sup> external data from patients treated at MD Anderson Cancer Center, patients treated in Nijmegen, Netherlands,<sup>[76]</sup> and most recently



with 4,202 patients from 8 international centers.<sup>[77]</sup> The UISS has been subsequently modified into a simplified system based on separate stratification of metastatic and non metastatic patients into low-, intermediate-, and high-risk groups.<sup>[78]</sup> This provides a clinically useful system for predicting postoperative outcome and provides a unique tool for risk assignment and outcome analysis to help determine follow-up regimens and eligibility for clinical trials.

The Mayo Clinic created an extensive outcome prediction model for patients with clear cell RCC who are undergoing a radical nephrectomy.<sup>[79]</sup> According to an analysis of data from 1,801 patients, TNM stage, tumor size smaller than 5 cm, nuclear grade, and the presence of histological tumor necrosis were all found to be independent predictors of survival. Histologic necrosis is defined as any degree of microscopic tumor necrosis exclusive of degenerative changes such as hyalinization, hemorrhage, or fibrosis. The presence of tumor necrosis has been recognized to be associated with markers of advanced disease,<sup>[79-81]</sup> as well as an independent predictor of survival.<sup>[79,81,82]</sup> These factors were combined into the stage, size, grade, and necrosis (SSIGN) scoring algorithm. Decreased survival was shown to correlate with an increased SSIGN score with scores of 0–1 and greater than 10 correlating with a 5-year cancer-specific survival rate of 99% and 7%, respectively.

In the metastatic setting, it is well accepted that PS is a strong predictor for survival. Similarly, several studies have shown that cancer-related symptoms were independent prognostic parameters in localized RCC.<sup>[83-85]</sup> Recently, a symptom-based classification was established and externally validated in a large multicenter series.<sup>[86,87]</sup> Based on symptoms at diagnosis, 388 renal tumors were stratified into three groups: asymptomatic tumors (S1), tumors with isolated local symptoms (S2), and tumors with systemic symptoms (S3). The S classification appeared to predict cancer-specific survival independent of tumor stage and grade. Two different large subsets of patients that integrated both tumor size and tumor-related symptom information within the TNM classification have resulted in improved prognostic stratification.<sup>[88,89]</sup> Karakiewicz, *et al.*<sup>[90]</sup> recently proposed a highly accurate (86.3%) prognostic nomogram that consisted of TNM stage, Fuhrman grade, tumor size, and symptom classification. External validation of the nomogram at 1, 2, 5, and 10 years after a nephrectomy revealed predictive accuracy of 87.8%, 89.2%, 86.7%, and 88.8%, respectively. Conversely, the UISS, which predicts cancer-specific survival rates at 2 and 5 years, was less accurate as evidenced by 86.1% and 83.9% estimates. Furthermore, the Karakiewicz model provides accurate predictions that span a 10-year period after a nephrectomy, which exceeds the prognostic range of other models.

The presence of distant metastases at diagnosis substantially changes the prognosis of patients with RCC.<sup>[91,92]</sup> Leibovich,

*et al.*<sup>[93]</sup> reported that in patients with non metastatic clear cell RCC who were treated with a radical nephrectomy, the median time to distant metastases was 1.3 years and of those who progressed to distant metastases, 77% died from RCC. Hutterer, *et al.*<sup>[94]</sup> recently developed a nomogram based on symptom classification and tumor size derived from a multi-institutional database aimed at quantifying the risk of distant metastases in patients with RCC. This nomogram was 85.2% accurate in predicting the individual probability of distant metastases in an external validation cohort and may assist in identifying patients at high risk of having metastatic RCC.

The outcome of patients with RCC nodal metastases is substantially worse than that of patients with localized disease. Hutterer, *et al.*<sup>[95]</sup> developed and externally validated a nomogram based on age, symptom classification, and tumor size that is accurate (78.4%) in predicting RCC nodal metastases in patients without radiographic evidence of distant metastases. This tool can help to risk adjust the need and the extent of nodal staging in patients without known distant metastases. More thorough staging can hopefully better select those in whom adjuvant treatment is necessary. As of today there are no clear guidelines regarding exactly who should be subjected to a staging lymphadenectomy with the intent of identifying those with nodal metastases. For example, Blom, *et al.*<sup>[96]</sup> demonstrated that in non metastatic T1-3 RCC patients, the rate of unsuspected lymph node metastases is as low as 3.3%. Such data indicate that the majority of RCC patients will be free of nodal metastases.

## MOLECULAR STAGING

Molecular biomarkers may prove more effective for predicting survival than traditional clinical parameters such as tumor stage and grade.<sup>[97]</sup> The next generation of prognostic models hopes to incorporate the advancements of molecular biology and genetics. Methods based on gene arrays, which screen for differential expression of thousands of genes, have identified large numbers of new, potentially important prognostic markers in RCC.<sup>[98-101]</sup> A useful tool for validating a limited number of biomarkers on a large patient population is the tissue microarray (TMA). Sections of the TMA provide targets for parallel *in situ* detection of DNA, RNA, and protein in the same set of specimens, which can be correlated to clinical data with respect to disease progression, treatment response, and survival. The evaluation of protein expression in a high-throughput TMA is a natural extension to the efforts for molecular staging. Accurate models for predicting survival can be constructed using multiple molecular biomarkers. Kim, *et al.*<sup>[102,103]</sup> have recently demonstrated that molecular characterization improves upon the UISS. Immunohistochemical analysis of 8 molecular biomarkers previously linked to the development of malignancies (Ki-67, p53, gelsolin, carbonic anhydrase [CA] IX, CA XII, PTEN [phosphatase and tensin homologue deleted on chromosome 10], epithelial cell adhesion molecule

[EpCAM], and vimentin) was performed on a custom TMA using clear cell RCC from 318 patients, representing all stages of localized and metastatic RCC. A prognostic model based primarily on molecular markers included metastasis status, p53, CA IX, gelsolin, and vimentin as predictors and had high discriminatory power; its statistically validated concordance index (C-index) was found to be 0.75. A prognostic model based on a combination of clinical and molecular predictors included metastasis status, T stage, ECOG-PS, p53, CA IX, and vimentin as predictors and had a C-index of 0.79, which was significantly higher than that of prognostic models based on grade alone (C = 0.65), TNM stage alone (C = 0.73), or the UISS (C = 0.76).

Two nomograms were proposed that could be used to predict disease-specific survival. One nomogram is based on metastasis status and molecular markers (CA IX, p53, vimentin, and gelsolin). The second nomogram combines clinical and molecular variables (metastasis status, T-stage, ECOG-PS, CA IX, p53, and vimentin). By including metastasis status, the nomograms accurately predict cancer-specific survival in patients with both localized and metastatic RCC. Both nomograms can be used to calculate 2- and 4-year cancer-specific survival rates as well as median survival. This study shows that accurate models for molecular staging of a solid tumor can be developed using a very limited number of markers. Although these nomograms are useful for visualizing our predictive models, they need to be validated on independent patient populations prior to being applied to patient care.

Gene expression analysis studies have also demonstrated the ability to define patient prognosis. Takahashi, *et al.*<sup>[104]</sup> showed that clear cell RCC tumors exhibited a high expression of VEGF and ceruloplasmin and down-regulation of kininogen. The authors identified 40 genes that identified patients with the best prognosis. Increased expression of SPROUTY, an angiogenesis inhibitor, was associated with a good prognosis, while loss of transforming growth factor beta receptor II and MMP-3 were associated with poor outcomes. Takahashi, *et al.*<sup>[105]</sup> also identified a unique gene expression profile in clear cell RCC that differentiated between patients who died from their disease and those with no evidence of metastasis. Jones, *et al.*<sup>[106]</sup> reported the ability of gene expression analysis within the primary tumor to identify a metastatic signature, which includes topoisomerase II $\alpha$  and glycosyl ceramide synthase. Vasselli, *et al.*<sup>[98]</sup> identified 45 genes to separate patients with metastatic RCC into groups based on prognosis. Increased expression of vascular cell adhesion molecule-1 was found to be particularly powerful in selecting patients with improved prognosis.

## CONCLUSIONS

Over the last 10 years, there has been a gradual transition from the use of solitary clinical factors as prognostic markers

for patients with RCC to the introduction of systems that integrate multiple factors to the introduction of molecular and genetic markers with the goal of improving patient prognostication. The field of RCC is rapidly undergoing a revolution led by molecular biomarkers. The understanding of tumor biology gleaned from molecular biomarker research will be critical to the future treatment of patients with RCC.

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