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Renal Cell Carcinoma: Where Will the State-of-the-Art Lead Us?

A. Rose Brannon and **W. Kimryn Rathmell**
Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC.

Abstract

Less than 20 years ago, the von Hippel-Lindau (VHL) gene was discovered and associated with sporadic renal cell carcinoma (RCC). Since then, researchers and clinicians have labored to better understand the biology driving RCC tumor progression and provide means to predict patient survival and response to therapy. Studies surrounding *VHL* inactivation and downstream effects continue to provide insights into these areas. Besides studies of this primary pathway, cytogenetic studies, gene expression analyses, tissue microarrays, serum proteomics, genomic resequencing, and microRNA profiling have yielded greater understanding of RCC biology and clinical presentation, and have led to a rich understanding of the heterogeneity of this disease. We review the current state of research investigations into the molecular biology of RCC, and discuss the applications to currently used clinical prognostic nomograms.

Introduction

One in 75 people will develop kidney cancer during their lifetime, being the seventh leading cause of cancer in men and eighth in women in the United States [1]. Renal cell carcinomas (RCCs) encompass a heterogeneous group of cancers including 60% to 80% of cases being histologically of the clear cell (ccRCC) subtype. Papillary and chromophobe histologies round out the other common subtypes. These stratifications represent highly dissimilar diseases and not strictly variants of RCC. Recently, an increased appreciation of the distinct biology of these subtypes has led to considerations of histology when managing these patients; however, even this major subdivision provides little immediate guidance regarding disease prognosis and management. Given this uncertainty, there is great need for both prognostic and predictive biomarkers.

Tremendous efforts have been expended in the search for reliable indicators of the underlying biology of renal carcinomas. With advancing technological opportunities to probe the genetic and molecular underpinnings of this cancer, many critical discoveries have led to major innovations in RCC, including a panel of molecularly targeted therapies which grew directly from these discoveries. Our appreciation of the genetic steps contributing to renal cancer development has been broadened, although some of the results have been surprising. However, RCC stands apart as a notoriously chemotherapy-resistant cancer that has been coaxed into submission using molecularly targeted agents that inhibit a target far removed from the inciting genetic lesion. The investigations leading to these advances are reviewed here and form a roadmap for future cancer therapeutic developments.

Correspondence W. Kimryn Rathmell 450 West Drive, CB 7295, Lineberger Cancer Center, Chapel Hill, NC 27599, USA. Rathmell@med.unc.edu.

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Additionally, modern treatment decisions and the future of RCC drug development can still benefit from increased understanding of the underlying tumor biology. Tremendous gains in the treatment of this cancer remain to be made. The state-of-the-art science of RCC is a continuously evolving topic, but one that promises to provide us with valuable tools for defining the unique biology of an individual's tumor to inform predictions about recurrence or response to therapy for patient-driven clinical decisions, and to aid in the discovery of new strategies to effectively target this cancer. This review focuses on the current understanding of RCC biology, focusing primarily on ccRCC, and examines genetic and molecular investigations that have led to some biomarkers currently being advanced to provide personalized approaches to patient care that extend beyond clinical features in current nomograms.

VHL and HIF Biology in ccRCC

The biology of the von Hippel-Lindau (*VHL*) gene product, pVHL, and its regulation of the hypoxia-inducible factor (HIF) family of dynamically regulated transcription factors, is indelibly linked to ccRCC biology. The discovery of the *VHL* gene, and its association with the VHL syndrome of central nervous system hemangioblastomas, pheochromocytoma, and ccRCC, in 1993 [2] led almost immediately to the discovery that *VHL* mutation is tightly associated with sporadic ccRCC as well [3,4]. The loss of *VHL* leads to the loss of regulation of HIF family members HIF1α and HIF2α [5], and several splice variants of HIF3α [6]. Xenograft studies have confirmed that restoration of pVHL expression or suppression of deregulated HIF impairs the growth of these tumors [7,8].

Because of the essential role of *VHL* in RCC, the presence and type of *VHL* mutations in tumors have been consistently considered as possible biomarkers. Cowey et al. [9] recently thoroughly reviewed its potential in prognosis and prediction. Further research is still required to establish *VHL*'s efficacy as a biomarker, but given the frequency of its inactivation, more hope may lie in looking downstream.

When *VHL* is inactivated and HIF expression thereby stabilized, a variety of other genes are transcriptionally upregulated [10]. Which of these factors or combination of factors participates in forming and maintaining the malignant phenotype of these tumors remains an open question. Certainly many hypoxia-responsive genes are outstanding candidates. One HIF target, the vascular endothelial growth factor (VEGF), has been found to be vastly upregulated in kidney tumors compared to its elevated expression in many other cancers [11,12]. This growth factor contributes to the highly vascular nature of this tumor, acting as a mitogen for tumor endothelial cells. Multiple therapeutic strategies have been developed to target VEGF, neutralizing its activity as a soluble growth factor or inhibiting the activated VEGF receptor tyrosine kinase. Remarkably, these strategies have consistently demonstrated an effect of inhibiting tumor progression, including therapeutic responses [13]. These breakthroughs demonstrate how much ccRCC remains dependent on key elements of HIF pathway activation, and that even if we can only target a fraction of the perturbed system, there can be tremendous clinical benefits.

We have also learned that in spite of the tremendous correlation of ccRCC with loss or inactivation of *VHL*, the effect on HIF deregulation is not uniform. Variant mutations in *VHL* may contribute to imbalances of HIF1a and HIF2a deregulation leading to distinct effects on cell growth [14,15]. Renal tumors can in fact be characterized as H1H2 (expressing HIF1a and HIF2a) or H2 (expressing only HIF2a), with dramatically differing effects on tumor cell metabolism and C-myc regulation [16••]. Recent evidence suggests that the H2 tumors may lose HIF1a expression as a result of nonsense missense mutations in a subset of tumors [17••], suggesting a potentially selective pressure to lose the HIF1a gene during tumor progression. These insights to potentially narrow the key tumorigenic events within the *VHL*/HIF axis will undoubtedly lead to novel strategies for prognostic and therapeutic maneuvers.

Cytogenetic Studies

Beyond *VHL* loss and HIF activation lies the great morass of genetic events that supplement these common molecular features to give the "teeth" to RCC. Major efforts have yet to identify a simple linear progression of genetic lesions accounting for the gains in aggressiveness in RCC. Rather, it appears that many events, most surprisingly dissimilar to other epithelial cancers, participate in this progression, discovered via both new strategies to examine the cancer genome and conventional cytogenetic studies. These studies have enhanced our understanding of the cancer genome in RCC.

Quite a bit of work has already been done to advance the field of RCC cytogenetic research [18–20]. However, two important large-scale ccRCC cytogenetics studies were published within the past year. One study performed both single nucleotide polymorphism (SNP) analysis and gene expression analysis on 54 cases of sporadic ccRCC and 36 tumors from 12 patients with VHL disease [21•]. Importantly, this group confirmed a widely held, but previously unproven assumption about ccRCC and VHL disease: tumors from sporadic and VHL-disease ccRCC tumors have overall similar profiles, but sporadic tumors are more heterogenous and contain more events per tumor. In fact, unsupervised analysis of gene expression data from these two groups could not distinguish them. While this study did not identify any prognostic or predictive biomarkers, knowing that VHL disease induced ccRCC and sporadic ccRCC tumors are so similar suggest that they may be able to be targeted with the same treatments.

The other study was a prospective study of 282 ccRCC patients with up to 108 months of follow-up using traditional cytogenetic karyotyping techniques [22••]. They determined that loss of 3p was significantly associated with increased disease-specific survival, while loss of 4p, 9p, and 14q were significantly associated with decreased disease-specific survival. Only loss of 9p remained significant in multivariable analysis in the presence of standard clinical measures, but the specific genes in these regions implicated in causing the poor prognosis remain to be characterized.

In determining these individual genes associated with RCC, we turn to sequencing studies. Although whole-scale sequencing has not yet been performed on large numbers of renal carcinomas, this tumor type is being examined as a priority tumor in the cancer genome atlas and by other international efforts. Large-scale sequencing of cancer genomes is becoming more common as technology becomes better and the cost decreases. In ccRCC, the Futreal group has resequenced 3544 genes in 96 pretreatment tumors, as well as performing SNP and gene expression analyses on these tumors [17••]. They then sequenced genes with at least two nonsynonymous mutations in another 246 ccRCC tumors. Using a false discovery rate cutoff of 20%, the authors suggest that mutations in SETD2, JARID1C, NF2, UTX, and MLL2 have been selected for a role in cancer development or progression, opening up several interesting themes in tumor progression, particularly pertaining to the role of histone methylation. These studies will likely enhance our understanding of the steps that may permit or promote renal tumorigenesis, ultimately to the benefit of patient-centered therapy.

Gene Expression Studies

Following the overwhelming success of gene expression analyses in breast cancer, including the resulting US Food and Drug Administration–approved gene panels predictive of risk for breast cancer recurrence [23], it was logical to attempt similar studies in ccRCC. Gene expression data of ccRCC tumors have been studied by both supervised and unsupervised analyses. Supervised analyses are designed to reveal the differences among tumors based on preselected criteria, often survival, easily deriving biomarkers for the clinical characteristic of interest. In contrast, unsupervised analyses work with the data a priori and, therefore, are more likely to determine the underlying biological differences. While these biological differences

may also correspond with survival or other clinical characteristics, these correlations are tangential to the original analyses; thus, these two types of analyses generate very different kinds of results. Table 1 gives an overview of the microarray gene expression studies performed in RCC.

Analyses focused on clinical outcomes

One of the earliest studies examined 29 ccRCC tumors and identified 51 genes that could classify tumors based on 5-year disease-specific survival [24]. This study verified the possibility that gene expression profiles could be used to predict outcome, but remains to be examined in a validation study or to be defined by biological parameters that may account for this difference in disease activity. Two years later, another group examining 51 metastatic clear cell tumors identified 45 survival genes, with vascular cell adhesion molecule-1 (VCAM-1) being the most predictive [25]. Since then, two retrospective studies have shown that VCAM-1 has prognostic significance [26,27]. Intriguingly, high expression of this molecule predicted for better overall survival for both clear cell and papillary histology, suggesting that VCAM-1 expression may generally indicate tumor cells with lower metastatic potential. The further implications for antiangiogenic therapy are not yet known.

Another study described a gene signature for RCC progression, including three genes (caveolin 1, lysl oxidase, and annexin A4) that had been previously associated with RCC aggression and/or survival [28]. A similar study concurrently identified a potential gene panel for aggressive clinical behavior in ccRCC by analysis of gene expression profiles of a set of nonaggressive (low Fuhrman grade), aggressive (mostly high Fuhrman grade), metastatic, and normal kidney samples [29]. One of these genes, survivin, was shown to independently predict clear cell progression and risk of death [30] and, therefore, was incorporated into a new prognostic algorithm [31].

The largest study included 177 clear cell tumors and identified 340 transcripts (including VCAM-1) that could be used to assign a risk score to a patient, which was significant in multivariate analysis with stage, grade, and performance status [32•]. When this group later investigated the biology associated with their survival gene set, they found that tumors from patients who survived longer more resembled normal renal cortex or glomerular tissue, while poor survival patients had tumors that exhibited a wound-healing signature [33]. Further delineation and validation of pathways that contribute to tumor progression and an enhanced appreciation of the originating cell of ccRCC would be extremely useful for modeling RCC and identifying pre-cancerous changes earlier.

Biologically driven analyses

While all of the above studies performed supervised analysis, many of them [24,25,28,29, 32•] started with an unsupervised analysis. A common practice in array analysis is to perform unsupervised analyses to get a general understanding of the data, then move on to a supervised analysis to achieve the answers sought. Two of the unsupervised analyses from above bear further examination: the study that identified VCAM-1 as a prognostic biomarker first showed that there seemed to be two subgroups within the stage IV tumors, with possible survival differences [25]. This suggests that molecular features beyond clinical staging could provide informative data in understanding even metastatic tumor behavior. The group of Zhao et al. [32•] examined their 177 tumors using 3674 genes and saw five different subgroups within two larger groups of ccRCC, with significant survival differences as well as predicted biological pathway distinctions. These studies helped set the stage for further delineation of subgroups within ccRCC.

In a strategy to intersect the supervised analyses with biological rationale directed toward the most studied and understood pathway in RCC, gene expression profiles were linked with VHL tumor suppressor protein (pVHL) mutation analysis and expression characteristics of the HIFs [16••]. In this study, 160 ccRCCs were classified as *VHL* mutant or wild type and according to HIF protein expression. *VHL* mutant, HIF1 and HIF2 expressing tumors (H1H2) overexpressed the Akt/mTOR pathway, while *VHL* mutant tumors expressing solely HIF2 (H2 tumors) replicated more rapidly, marked by overexpression of Ki-67 and activation of c-Myc signaling. While survival data were not available for this study, other groups have identified Ki-67 as a poor-risk marker [34]. Further studies on the efficacy of HIF1 profile as a prognostic marker are anticipated.

Two other studies stand out as being predominantly geared toward identifying the inherent subgroups and underlying biological differences of ccRCC. The first is the Skubitz group [35], which looked at 16 ccRCC tumors and saw that there seemed to be two types of clear cell, one that more highly overexpressed metabolic genes and the other extracellular matrix/cell adhesion genes. Most recently, we used a robust technique called unsupervised consensus clustering on 48 tumors to identify two subtypes of ccRCC, ccA and ccB, that could be distinguished by fewer than 120 probes [36]. Validating these results in the Zhao et al. [32•] dataset of 177 tumors, we determined that patients with ccA tumors have a marked survival advantage over those with ccB tumors. Additionally, this dataset shares the characteristics that ccA tumors display a profile of altered metabolism, whereas ccB tumors display characteristics of wound healing and epithelial to mesenchymal transition. This classification scheme was significantly associated with survival in both univariate and multivariate analysis and is undergoing further validation.

A large number of potential biomarkers have emerged from all these gene expression studies. Encouragingly, trends are beginning to emerge between studies. The next important step will be bringing these potential biomarkers and biomarker profiles to the clinical arena, an aspect discussed in the Nomograms section below.

Other Technologies

A number of other technologies have been utilized in attempting to find good prognostic biomarkers for ccRCC. Among them, we will touch briefly on tissue microarrays (TMAs), plasma serum protein analysis, and microRNA profiling.

TMAs allow for quantitative and relatively quick immunohistochemical (IHC) analysis of tumor protein expression patterns. A total of 800 organ-confined ccRCC tumors were recently examined for expression of 15 proteins with regard to tumor stage, Fuhrman grade, and survival data [37]. Surprisingly, while pVHL and phospho-mTOR staining correlated inversely with tumor stage and grade, neither protein correlated with survival. However, expression of p27, PAX2, periostin, p-S6, and CAIX did correlate with 5-year survival. Within the intermediate-stage tumors (pT2 and pT3), they found that patients with p27 and CAIX-positive tumors fared better. This information could be very useful in making clinical decisions for patients in these difficult to predict categories. Many other potential biomarkers have been identified through other TMA studies [34].

All of the potential biomarkers listed thus far require removal and processing of at least part of the tumor. In contrast, the use of plasma serum proteins would simply require a blood test. Plasma serum proteins have traditionally been studied to find noninvasive diagnostic markers for the presence of ccRCC as compared with normal or benign renal tissue. To date, no measurable proteins have been moved forward for screening or diagnostic evaluation. However, work from Perez-Gracia et al. [38] identified potential predictive biomarkers for response to sunitinib in metastatic RCC patients. Serum from patients with clinical response

or progression was screened by cytokine arrays to discover that tumor necrosis factor-α and matrix metalloproteinase-9 levels remained low in responders. Additionally, high levels of these proteins in the serum correlated with decreased overall survival. In another study, low levels of sVEGFR-3 and VEGF-C in the serum corresponded with longer progression-free survival and objective response rate in bevacizumab-refractory metastatic RCC [39]. A third study suggested that large changes in serum VEGF, sVEGFR-2, and sVEGFR-3 levels corresponded with tumor response [40]. All of these potential predictive biomarkers require external validation in larger sample sizes, but suggest that serum may prove to contain cogent markers of survival and response.

MicroRNA, 21–23 nucleotide segments of single-stranded non-coding RNA, have now been implicated in tumorigenesis of many cancers, even being identified as potential prognostic biomarkers in several of these. The aberrant expression of these non-coding RNAs can provide a powerful method of epigenetic tumor regulation, as an individual microRNA can alter the expression of many target genes. In RCC, various studies have identified various individual or panels of microRNAs that are differentially expressed between normal renal tissue and tumor [36,41–43] or between histological subtypes [41,44]. The identification of relevant targets of these tumor-associated microRNAs is just becoming realized [41,45]. What makes microRNAs so unique compared to proteins and other small molecules is that their stem-loop structure makes them extremely stable. MicroRNAs can be easily extracted from formalin fixation, paraffin-embedded tissue, and blood. The ability to easily use noninvasive measures to identify a stable target makes microRNAs a very attractive biomarker for diagnostic, prognostic, and predictive purposes.

Updating Nomograms

There are a number of prognostic scoring systems to assign risk for death to ccRCC patients already in common use based on clinical variables. An understanding of these patient stratification schemes is necessary as the field moves toward the routine incorporation of molecular biomarkers into strategies for patient stratification. For initial prognostication of risk for recurrence or death following a definitive surgical procedure, the American Joint Committee on Cancer Tumor Node Metastasis (TNM) [46], the UCLA Integrated Scoring System (UISS) [47], and the Memorial Sloan-Kettering Cancer Center (MSKCC) [48] nomograms all use clinical information including radiographic size and clinical performance status, and add in histologic information to the noninvasive clinical measures. The Mayo Clinic's Stage, Size, Grade, and Necrosis (SSIGN) algorithm further includes tumor necrosis [49], and another nomogram from MSKCC uses all of the above and vascular invasion [50]. Thus, eventual transitions to inclusion of molecular information to the clinical scenario will be relatively straightforward once the most relevant molecular biomarkers emerge.

For prognosticating survival in the metastatic setting, a metastatic disease MSKCC score is one of the most commonly used algorithms, incorporating blood measurements of hemoglobin, serum calcium, and lactate dehydrogenase, as well as clinical evaluation of performance status and nephrectomy status [51]. A similar nomogram was identified by the Cleveland Clinic Foundation based on an independent multivariate analysis [52]. The Mayo Clinic devised a nomogram for metastatic clear cell tumors only that scored patients based on symptoms at nephrectomy, bone/liver metastases, multiple metastases, resection of all metastases, time to progression, tumor thrombus, primary tumor grade, and coagulative tumor necrosis [53]. A recent outstanding review by Isbarn and Karakiewicz [54•] provides a complete overview of these nomograms.

Each of the above means of calculating risk for recurrence or death of disease were designed after 1999 and are well used by clinicians, yet have not included any of the large number of

possible biomarkers. In 2005, Kim et al. [55] devised a prognostic model to assess patients' metastatic disease that added CA9, vimentin, p53, and pTEN IHC quantification to the common measure of tumor stage and patient performance status. This model had a slightly higher concordance index than did the UISS scale using clinically available parameters (0.68 vs 0.62). While not making a substantial stride in influencing prognostic accuracy, this study opened the door to hybrid nomograms that incorporate both clinical and genetic or molecular features. Table 2 provides a list of clinical features incorporated into commonly used algorithms that should be considered when designing hybrid nomograms.

More recently, Yao et al. [27] fashioned a three-gene signature of VCAM-1, EDNRB, and RGS5 to be measured by quantitative real-time polymerase chain reaction. Their outcome prediction score could stratify patients into low, medium, and high-risk groups, even in metastatic disease cases. However, while the authors calculated a receiver operating characteristic curve to predict the specificity and sensitivity of their predictor alone and with tumor stage and grade, it remains necessary to be validated in direct comparison with a currently used algorithm. Similarly, the Bioscore algorithm was formulated in 2009 based on IHC expression of B7-H1, survivin, and Ki-67 [31]. The authors found that dichotomizing the expression levels of these proteins provided a c-index of 0.733, suggesting that Bioscore may add prognostic value to both the UISS and SSIGN algorithms. The Bioscore group presents an algorithmic model that may be beneficial for other groups to mimic: identifying patient groups not prognostically improved by the addition of Bioscore data, such that only groups that would benefit were recommended for further testing. This system is appropriate to avoid undue testing expenses, and inappropriately applying molecular information in scenarios where the additional data are uninformative.

While all of the above biomarker algorithms may enhance prognostic ability, they lack the ability to address underlying tumor biology. The Pantuck group has begun to address tumor biology by developing a nomogram with a c-index of 0.89 that includes TNM staging, Fuhrman grade, and loss of chromosome 9p [22••]. The incorporation of biological information into existing nomogram strategies for clinical prognostication or prediction of response to therapy is clearly not trivial. However, neither clinical data, nor biological information, can be treated in isolation. Both are relevant to patient care and patient outcomes. The future success of biomarker programs will take a considered approach to modifying existing algorithms or developing new hybrid algorithms based on large-scale multivariate analysis.

Conclusions

In the last decade, great strides have been made for RCC patients with regard to earlier diagnoses, development of new treatment options, providing better prognostic information, and beginning work on predictive biomarkers. Many challenges remain: most of the new prognostic algorithms still require independent validation, ideally in prospective studies. The large number of biomarkers needs to be culled into a manageable panel of markers for clinical application in prognosis and prediction, made widely available, and covered by health insurance. However, breast cancer has proven to us that these seemingly overwhelming tasks are very possible. RCC is ripe for personalized cancer treatment, which takes into account the underlying biology of an individual's tumor. The state-of-the-art has clearly led this field to the enviable position of having a range of effective molecularly targeted therapies, with further improvements expected on the horizon; mature profiles of protein and nucleic acid biomarkers, which will help us to define the spectrum of tumors that lie under the umbrella of ccRCC; and a future unmapped territory of genetic mutations to explore that may provide more tools and answers to the questions we ask. There is great hope for the future of RCC treatment, and it will be exciting to see what new advances will be made in the decade to come.

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Table 1

Gene expression studies in RCC

Study	Year	Samples	Analytical focus	Results
Clinically driven analyses				
Takahashi et al. [24]	2001	29 cc 29 normal	5-year survival	51 probes associate with survival, 96% accuracy
Vasselli et al. [25]	2003	51 cc 6 papillary 1 unknown	Survival	45 genes most associated with survival; VCAM-1 alone can stratify patients by survival
Jones et al. [28]	2005	22 cc 10 metastases 37 other 24 normal	Progression and metastases	31 genes that are continuously deregulated in disease progression; 155 genes that associate with metastases, 88.9% accuracy
Kosari et al. [29]	2005	10 aggressive cc 9 non-aggressive cc 9 metastatic cc 12 normal	Tumor aggressiveness	35 genes distinguish between non-aggressive and aggressive tumors; survivin expression associated with survival by multivariate analysis in 183 patients
Zhao et al. [32•]	2006	177 cc	Unsupervised	2 primary clusters composed of 5 subclusters with survival difference
Yao et al. [27]	2008	25 cc (14 metastatic) 2 metastases	Metastatic vs nonmetastatic	3 genes (VCAM-1, EDNRB, RGS5) that by qRT-PCR associate with survival
Biology-driven analyses				
Vasselli et al. [25]	2003	51 cc 6 papillary 1 unknown	Unsupervised	2 clusters of metastatic tumors with survival difference
Skubitz et al. [35]	2006	16 cc 21 normal	Unsupervised	2 subtypes distinguishable by 546 genes, with possible pathway differences
Zhao et al. [32•]	2006	177 cc	Survival	259 genes associated with survival by univariate and multivariate analysis
Gordan et al. [16••]	2008	21 cc	Wild-type *VHL* vs H1H2 vs H2 tumors	3 groups have distinct biological pathways; H2 tumors overexpress c-Myc, leading to increased proliferation
Zhao et al. [33]	2009	177 cc	Biology of survival gene set	Good prognosis tumors resemble normal renal cortex or glomerulus; poor prognosis tumors associated with wound healing and loss of differentiation gene sets
Brannon et al. [36]	2010	48 cc 18 normal	Unsupervised consensus clustering	2 subtypes of cc (ccA and ccB) with pathway and survival differences, differentiable by < 120 probes
Gene expression and cytogenetics/sequencing analyses				
Furge et al. [18]	2004	60 cc 5 papillary 16 chromophobe	Histological classification by virtual cytogenetics	1018 gene classifier and cytogenetic classifier to distinguish between 3 subtypes, 99% and 81% accuracy, respectively
Sultmann et al. [19]	2005	65 cc 13 papillary 9 chromophobe	Cytogenetics; metastases and survival	136 genes significantly associated with cytogenetic abnormalities; 45 genes

Study	Year	Samples	Analytical focus	Results
		25 normal		associated with survival; 85 genes associated with metastasis formation
Beroukhim et al. [21•]	2009	49 sporadic cc 5 metastases 36 VHL tumors	VHL disease vs sporadic clear cell	VHL disease and sporadic clear cell tumors have similar gene expression and cytogenetic profiles, but sporadic cases have more frequent alterations
Dalgliesh et al. [17••]	2010	96 cc	Genetics by sequencing	Mutations in histone modification and DNA damage repair genes may be important in RCC development or progression

cc—clear cell; H1H2—HIF-1 and HIF-2 overexpressing; H2—HIF-2 only overexpressing; PCR—polymerase chain reaction; RCC—renal cell carcinoma; VCAM—vascular cell adhesion molecule; VHL—von Hippel Lindau.

Table 2

Clinical features from RCC nomograms predictive for recurrence or survival

Marker	Nomogram	Year	n	Histology	Stages
Patient characteristics					
Bone/liver metastases	Mayo [53]	2005	727	Clear cell	Metastatic
Hemoglobin	MSKCC [51]	1999	670	All	Metastatic
Multiple metastases	Mayo [53]	2005	727	Clear cell	Metastatic
Nephrectomy	MSKCC [51]	1999	670	All	Metastatic
Presence of hepatic/pulmonary/lymph node metastases	Cleveland Clinic [52]	2005	353	All	Metastatic
Prior radiotherapy	Cleveland Clinic [52]	2005	353	All	Metastatic
Resection of metastases	Mayo [53]	2005	727	Clear cell	Metastatic
Serum calcium	MSKCC [51]	1999	670	All	Metastatic
	Cleveland Clinic [52]	2005	353	All	Metastatic
Serum LDH	MSKCC [51]	1999	670	All	Metastatic
	Cleveland Clinic [52]	2005	353	All	Metastatic
Symptoms/performance status	MSKCC [51]	1999	670	All	Metastatic
	MSKCC [48]	2001	601	All	Localized
	UISS [47]	2001	661	All	All
	Mayo [53]	2005	727	Clear cell	Metastatic
	MSKCC [50]	2005	701	Clear cell	Localized
Time to progression	Mayo [53]	2005	727	Clear cell	Metastatic
Time to study entry	Cleveland Clinic [52]	2005	353	All	Metastatic
Tumor characteristics					
Grade	UISS [47]	2001	661	All	All
	SSIGN [49]	2002	1801	Clear cell	All
	Mayo [53]	2005	727	Clear cell	Metastatic
	MSKCC [50]	2005	701	Clear cell	Localized
Histology	MSKCC [48]	2001	601	All	Localized
Microvascular invasion	MSKCC [50]	2005	701	Clear cell	Localized
TNM stage	AJCC [56]	2005	1065	All	Localized
	MSKCC [48]	2001	601	All	Localized
	UISS [47]	2001	661	All	All

Marker	Nomogram	Year	n	Histology	Stages
	SSIGN [49]	2002	1801	Clear cell	All
	MSKCC [50]	2005	701	Clear cell	Localized
Tumor necrosis	SSIGN [49]	2002	1801	Clear cell	All
	Mayo [53]	2005	727	Clear cell	Metastatic
	MSKCC [50]	2005	701	Clear cell	Localized
Tumor size	MSKCC [48]	2001	601	All	Localized
	SSIGN [49]	2002	1801	Clear cell	All
	MSKCC [50]	2005	701	Clear cell	Localized
Tumor thrombus	Mayo [53]	2005	727	Clear cell	Metastatic

AJCC—American Joint Committee on Cancer; LDH—lactate dehydrogenase; MSKCC—Memorial Sloan-Kettering Cancer Center; RCC—renal cell carcinoma; SSIGN—Stage, Size, Grade, and Necrosis; TNM—tumor node metastasis; UISS—UCLA integrated scoring system.