STATE OF THE ART REVIEW

Renal cell carcinoma

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ABSTRACT

The treatment of renal cell carcinoma (RCC) has changed greatly over the past 15 years. Progress in the surgical management of the primary tumor and increased understanding of the molecular biology and genomics of the disease have led to the development of new therapeutic agents. The management of the primary tumor has changed owing to the realization that clean margins around the primary lesion are sufficient to prevent local recurrence, as well as the development of more sophisticated tools and techniques that increase the safety of partial nephrectomy. The management of advanced disease has altered even more dramatically as a result of new agents that target the tumor vasculature or that attenuate the activation of intracellular oncogenic pathways. This review summarizes data from prospective randomized phase III studies on the surgical management and systemic treatment of RCC, and provides an up to date summary of the histology, genomics, staging, and prognosis of RCC. It describes the management of the primary tumor and offers an overview of systemic agents that form the mainstay of treatment for advanced disease. The review concludes with an introduction to the exciting new class of immunomodulatory agents that are currently in clinical trials and may form the basis of a new therapeutic approach for patients with advanced RCC.

Introduction

The investigation and management of renal cell carcinoma (RCC) has undergone an unprecedented period of change. This is largely due to advances in genomics and biological discoveries that can be successfully targeted to benefit patients. Pivotal to these advances was the recognition of mutations of the von Hippel-Lindau gene, and resultant stabilization of the hypoxia response pathway as a major driver of clear cell type RCC. Numerous new therapies are emerging or available based on this discovery, and new concepts regarding disease management to avoid overtreatment or toxicity are being considered. The pace of new findings continues unabated, making regular, comprehensive updates essential both to stay current with the evolving literature and standards, and to be poised and ready to adapt to the coming changes as this field continues to advance.

Incidence and prevalence

Worldwide, RCC is the ninth most common cancer, with about 337 860 new cases diagnosed in 2012. In 2013, cancers of the kidney and renal pelvis were estimated to occur in 65 150 patients in the United States, resulting in 13 680 deaths. In the World Health Organization Europe region, an estimated 121 629 new cases of RCC occurred in 2012, of which 75 676 affected men. The incidence of RCC varies geographically (fig 1), with the highest incidence in developed countries. The reason for the higher incidence in developed countries and in men is not clear. Genomic, occupational, and other environmental exposures such as smoking have been implicated. With the increased use of abdominal imaging for screening and diagnostic purpose, incidental renal masses and RCCs are being discovered more often. In a recent review of 3001 patients without symptoms being imaged for computed tomography colo-nography, 14% of patients harbored a renal mass greater than 1 cm in size.

Classification of RCC

In the past decade it has become clear that not all RCCs are related. It is no longer appropriate to lump these diseases together in clinical trials or in the consciousness of practising oncologists and urologists. This section will briefly define the diseases that fall under this umbrella and the implications for surgical and medical management. It will also provide a brief overview of their genetic features.

RCC and other diseases arising in the kidney

We deliberately avoid the term “subtype,” which refers to a subordinate grouping within a general classification. Rather, we will refer to these cancers as the independent entities that they are. We will describe clear cell, papillary, and chromophobe renal cell carcinomas and will briefly

SOURCES AND SELECTION CRITERIA

We searched PubMed from 1995 to 2014 using the keywords “renal cell carcinoma”, “RCC”, “histology”, “partial nephrectomy”, “sorafenib”, “sunitinib”, “pazopanib”, “bevacizumab”, “axitinib”, “temsirolimus”, and “everolimus”. References were prioritized to include prospective randomized phase III trials, followed by prospective randomized phase II trials. Selected retrospective peer reviewed studies were included if no prospective data were available on the topic. Material from abstracts was not included.
review several rare cancers that are also found in the kidney (collecting duct carcinoma, renal medullary carcinoma, and urothelial carcinomas). Several benign lesions of the kidney will also be discussed because they may mimic RCC or complicate its management. Detailed descriptions of the histologic diagnosis of these cancers can be found elsewhere, along with recently updated grading recommendations.

**Clear cell RCC**

These cancers make up about 70% of all cancers of the kidney. Histologically, they are defined by clear cytoplasm, with nested clusters of cells surrounded by a dense endothelial network.

**Papillary RCC**

This is the second most common tumor. Two subtypes of papillary renal cell cancer have been recognized—papillary type 1 and papillary type 2. Diagnosis is mostly based on features of papillary architecture. Cells typically display a basophilic cytoplasm, and the presence of foamy histiocytes is characteristic.

**Chromophobe RCC**

These tumor cells have a largely empty cytoplasm, typically have characteristic perinuclear clearing, and often feature a low mitotic rate. In general, these tumors have the lowest risk of developing metastases.

**Rare tumors of the nephron and collecting system**

Each of these tumor types occurs in less than 5% of cases. Renal cell carcinomas are thought to be derived from the tubules, with regional variance in the site of origin. However, tumors also arise from the cells and tissues that make up the renal medulla and collecting system. These tumors—collecting duct carcinoma, renal medullary carcinoma, and urothelial carcinoma—are highly distinct disease entities that bear little resemblance to RCCs. No strict standards of care exist for their management.

**Premalignant and benign lesions arising in the kidney**

Finally, various non-neoplastic conditions in the kidney give rise to masses that can share radiographic findings with renal cancers. These include angiomyolipomas—sarcomatous change lesions that can grow to a large size and can cause spontaneous hemorrhage. In addition, oncocytomas, which have low malignant potential, share many cytological and biological features with chromophobe-type renal cell carcinoma and can complicate the diagnosis on biopsy specimens.

**Key mutations and genomic features of renal derived carcinomas**

**Clear cell RCC**

This cancer has recently been defined in *The Cancer Genome Atlas*. The genetic feature most closely associated with this...
of heterozygosity, in a large group of chromatin remodelling
geneces. The most commonly inactivated genes include PBRM1, BAP1, and SETD2, although mutations in a variety of additional histone modifiers (KDM5a, ARID1a, and UTX) are also seen.\textsuperscript{15–18}

The impact of these mutations on the outcomes and biological
properties of these cancers is only now being identified,\textsuperscript{19–21} with recent evidence pointing to an association between SETD2 mutations and changes in chromatin packaging. Finally, mutations in genes associated with mTOR pathway signaling (PIK3CA, PTEN, and MTOR) have also been identified in a substantial proportion of tumors.

**Papillary RCC**

Much less is known about this tumor type. Two familial syn-
dromes are associated with increased risk of papillary-type renal
cell carcinoma. Mutations in the MET proto-oncogene predispose people to multifocal papillary type I RCC.\textsuperscript{22} In addition, the syndrome of hereditary leiomyomatosis and renal cell carcinoma (HLRCC)—caused by mutations in the fumarate hydratase (FH) gene—carries a risk for familial type II papillary RCC.\textsuperscript{23}

Although sporadic tumors in this disease group often fall into the papillary types I and II histological groups, it is not clear that they carry the same mutations as their hereditary counterparts. The results of large scale genomic profiling studies will be available soon.

**Chromophobe RCC**

Most of these tumors harbor chromosomal losses, including losses of whole chromosomes 1, 2, 6, 10, 13, 17, and 21,\textsuperscript{24} although the effect of these massive losses of DNA content remain uncertain. Except for mutations in PTEN, located at 10q23, and TP53, located at 17p13, few other mutations in tumor suppressor genes have been identified in chromo-
phobe RCC. The familial syndrome of chromophobe tumors is linked to Birt-Hogg-Dube syndrome,\textsuperscript{25} which is caused by germline mutations in the folliculin gene, FLCN.\textsuperscript{26}

**Rare tumours**

These include unclassified tumors, which may be misclas-
sified cases of the RCC subtypes described above, as well as collecting duct carcinoma, urothelial tumors (a variant of transitional cell carcinoma), and renal medullary carci-
noma. Renal medullary carcinoma is found exclusively in patients with a hemoglobinopathy, most commonly sickle cell trait, and is characterized by loss of expression of the chromatin regulatory gene SNF5/INI-1.\textsuperscript{27} Very little informa-
tion has been isolated from the genome to enable a better understanding of the pathophysiology of these tumors.

**Staging and prognosis of RCC**

The most commonly used staging system for RCC is the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) system (fig 2). This system was last revised in 2010 and contains three components: T indicates the size of the primary tumor and extent of invasion; N describes the status of metastasis to regional lymph nodes; and M indicates whether there is distant metastasis.\textsuperscript{28} Numbers or let-
ters appearing after T, N, and M subcategorize the size of the tumor or extent of disease.
TNM information is combined to assign an overall anatomic stage of I-IV, which correlates with prognosis. Patients with stage I RCC have a five year disease specific survival of about 80-95%; patients with stage II RCC have a five year disease specific survival of around 80%.29 In patients with stages I-II RCC, tumor invasion of the urinary collecting system is associated with significantly worse prognosis—five year survival is only about 60% compared with over 90% in those without invasion.10 For patients with stage III RCC, five year survival is about 60%.23 During the cytokine era, from the late 1980s to 2006, patients with stage IV RCC had a five year disease specific survival of less than 10%, with a median overall survival of 10-15 months.31-33 However, with the development of targeted agents, the median overall survival in patients with stage IV RCC has been extended beyond two years.34

**Management of localized disease**

About three quarters of people with RCC present with localized disease, and definitive local treatment remains the gold standard for managing patients with no evidence of distant metastasis.35 The incidence of small (<4 cm) renal masses has risen and the question of how to manage these lesions is now a daily dilemma for urologists.36 This has led to new considerations and conversations about management strategies that incorporate biopsy or surveillance of lower risk lesions.37-39

**Nephrectomy (partial vs radical) and laparoscopy**

Partial or radical nephrectomy remains the gold standard for the management of renal masses. The selection of tumors for partial nephrectomy has long been dictated by the anatomic location of the tumor, tumor stage, or other features that limit the potential for a complete tumor resection. Randomized clinical trials have examined the potential for nephron sparing approaches to preserve kidney function and reduce the long term morbidity associated with having a solitary kidney.40 In the final analysis of these results, the intention to treat analysis showed 10 year overall survival of 81.1% for radical nephrectomy and 75.7% for nephron sparing surgery. With a hazard ratio of 1.50 (95% confidence interval 1.03 to 2.16), the test for non-inferiority was not significant (P=0.77) but the test for superiority was significant (P=0.03), favoring radical nephrectomy. However, in patients with RCC who met all of the histopathological and clinical eligibility criteria, the difference was less pronounced (hazard ratio 1.43 and 1.34, respectively) and the superiority test was no longer significant (P=0.07 and P=0.17, respectively). Only 12 of 117 deaths were the result of RCC (four radical nephrectomy and eight partial nephrectomy), and 21 patients progressed (nine after radical nephrectomy and 12 after nephron sparing surgery).41 Results favored partial nephrectomy for preservation of renal function.42 Therefore, recently published guidelines recommend partial nephrectomy, when anatomically feasible, or radical nephrectomy when appropriate.35

Laparoscopic procedures have emerged because they provide improved postoperative recovery for patients and greater surgical operative field visibility for surgeons. Various studies have compared standard laparoscopy with robotic laparoscopy and have shown that laparoscopic partial nephrectomy is associated with an increased rate of conversion to radical nephrectomy when compared with robotic techniques (11.5% v 1%; P<0.001) and a greater decrease in estimated glomerular filtration rate (16.0% v 12.6%; P=0.03). No significant differences were seen with respect to warm ischemia time, estimated blood loss, transfusion rate, or postoperative complication.43 Cost comparison models currently favor the non-robotic standard laparoscopic approach.44

**Ablative approaches**

Ablative therapies have seen an increase in use and acceptance for a variety of reasons. A comprehensive review of each technology is not possible and can be found elsewhere.45-51 Renal masses can be managed with definitive radiofrequency ablation, including new microwave ablation, cryoablation, and stereotactic radiation. The effect on the tumor is unclear because evidence of viable tumor cells has been found on post-ablation histological examination, even when radiographically the tumor appears to be fully ablated. No randomized studies have compared ablative therapies with nephrectomy or directly compared the ablative options themselves. However, owing to the limited invasiveness of ablative techniques, they have an important role in managing small renal masses in patients whose comorbidities or other factors preclude surgical intervention.

**The controversy of mandatory node dissection**

In most other cancers, it is standard practice to assess local lymph nodes for evidence of disease spread, with sentinel lymph node analysis or extensive nodal dissection being essential for accurate staging of disease. However, although draining nodes in the retroperitoneum are commonly affected in advanced stages of disease, the routine collection of clinically uninvolved nodes is not standard practice across leading institutions. The European Organisation for Research and Treatment of Cancer (EORTC) investigated this in a randomized phase III trial, which found cancer in about 4% of resected nodes, and no difference in morbidity or long term outcomes with lymph node resection.52-54 Patients must continue to be considered on a case by case basis, and the resection of apparently involved nodes remains an important part of the care of patients with resectable locally advanced disease.

**Risk factors for progression**

Several clinical algorithms have been evaluated and validated for predicting the risk of developing recurrence after definitive local treatment. One of the first is the still widely used Leibovich prognostic score, which incorporates tumor size, stage, grade, histologic necrosis, and regional lymph node status in an algorithm designed to assess risk for developing metastatic disease.55 Other models include the Mayo clinic stage, size, grade, and necrosis (SSIGN) model55; the University of California, Los Angeles integrated staging system (UISI), which quantifies stage, tumor grade, and performance status56-58; and other preoperative clinical risk algorithms.59-61 A recent review of algorithms compared these tools.62

Although many biological and genetic features of renal cell carcinoma have recently been identified, none has yet been prospectively validated as risk factors. As our knowl-
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Three or more factors have a high risk of recurrence or other outcomes are not known. 

Cytoreductive nephrectomy
In the US, about 17% of patients diagnosed with de novo RCC present with metastatic disease. Two randomized phase III studies published in 2001 showed an improvement in survival for patients with metastatic RCC who underwent cytoreductive nephrectomy before treatment with interferon alfa. A review of SEER data showed that the proportion of patients who underwent cytoreductive nephrectomy gradually increased from 1993 to 2004, from 29% to 39%, then dropped slightly to 34% in 2010. A prospective randomized study assessing the effect of cytoreductive nephrectomy in patients treated with sunitinib was still accruing patients at the time of writing (NCT00930033).

Prognostic algorithms for patients with metastatic disease
A retrospective analysis at the Memorial Sloan Kettering Cancer Center (MSKCC) assessed 670 patients with metastatic RCC who received immunotherapy. A prognostic algorithm was then developed by performing a multivariable analysis of a series of clinical and laboratory parameters. Five independent adverse features were ultimately included in the algorithm (fig 3): 

- Karnofsky performance status of less than or equal to two 
- Less than one year between diagnosis and first systemic treatment 
- Hypercalcemia 
- Anemia 
- Lactate dehydrogenase more than one and a half times the upper limit of normal.

Patients with none of the five negative features had a median survival of 30 months, whereas those with three or more had a median survival of 4.8 months. A few years later, a similar analysis was performed on 645 patients who subsequently received molecularly targeted therapy, and a six component algorithm was derived. As in the MSKCC algorithm, it contained performance status, anemia, hypercalcemia and time from diagnosis to treatment, but instead of lactate dehydrogenase it included thrombocytosis and leukocytosis. This algorithm also separated patients into prognostically distinct categories.

Currently available systemic drugs
Three major categories of systemic drugs are currently being used to treat metastatic RCC: cytokines, drugs that target the VEGF pathway, and mTOR inhibitors.
FDA approval. Because of the rigors of receiving high dose IL-2, the patient population was highly selected—patients had excellent performance status, robust lung and cardiac function, and an age of less than 70 years. Two prospective randomized phase III studies published in 2003 and 2005 confirmed the complete response rate, but also found a 1% death rate from treatment related toxicity.\textsuperscript{76, 77} The first randomized trial found a higher response rate and complete response rate with high dose IL-2 (21% and 7%) than with low dose IL-2 (13% (P=0.048) and 4%), but no difference in overall survival, probably because the trial was not powered to assess the subset of the study population with a complete response.\textsuperscript{76}

Similarly, in the second randomized trial,\textsuperscript{77} the response rate was 23.2% for high dose IL-2 versus 9.9% for subcutaneous IL-2 plus interferon (P=0.018). No difference in overall survival was seen between arms. Efforts to identify predictive biomarkers for response to high dose IL-2 have so far been unsuccessful, and no published prospective reports provide guidance on how to select patients who may benefit from this treatment.

Interferon alfa was the mainstay of treatment for patients with metastatic RCC until the advent of targeted therapies, with two randomized prospective phase III studies showing a modest survival advantage for patients who received interferon compared with placebo.\textsuperscript{78, 79} Interferon was clearly inferior to most of the newer agents in terms of progression-free survival (PFS) measures and was poorly tolerated. This led to interferon being phased out as a treatment for patients with metastatic RCC except in combination with bevacizumab.

**Drugs that target the VEGF pathway**

The discovery of the \textit{VHL} mutation in patients with VHL disease,\textsuperscript{1} followed by the finding that somatic \textit{VHL} mutations occur in most sporadic clear cell RCCs,\textsuperscript{80} led to the development of agents that target circulating VEGF and VEGF receptors.

Five agents have been approved by the FDA for the treatment of metastatic RCC,\textsuperscript{81-86} including the intravenously administered VEGF inactivating antibody bevacizumab, and the orally bioavailable small molecule VEGF receptor inhibitors sorafenib, sunitinib, pazopanib, and axitinib. These agents vary in the number of addition tyrosine kinases that they target and the avidity with which they bind and inactivate the VEGF receptor (fig 4).\textsuperscript{87} These agents are thought to target the tumor endothelium and to have minimal effect on the tumor cells.\textsuperscript{88} A striking finding in patients treated with these agents is the association between treatment emergent or antecedent hypertension and improved patient survival.\textsuperscript{89} Figure 5 summarizes the differences in overall survival in patients who experienced treatment emergent hypertension versus those who did not. The biological drivers of this phenomenon have not been elucidated, but the findings raised important questions about the value of dose intensity for agents that target the VEGF pathway. As described in the axitinib section below, recent data suggest that increasing the dose beyond a certain threshold improves overall response rate but not PFS, and neither does it result in a higher complete response rate.\textsuperscript{90}

**Cytokines**

High dose interleukin 2 (IL-2) was approved by the FDA in 1992. Approval was based on a series of phase II studies describing the outcome of 250 patients treated with 600 000-720 000 IU per kg given intravenously every eight hours for a maximum of 14 doses per cycle.\textsuperscript{75} Patients showed an overall response rate (sum of partial and complete response rates) of 15% and a complete response rate of 5%. Most complete responses achieved with high dose IL-2 were durable, which provided the main impetus for
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PFS was 11.1 months for patients who received pazopanib versus 2.8 months for the placebo group (0.40, 0.27 to 0.60; P<0.0001). A subsequent trial of 1110 patients compared pazopanib with sunitinib as first line drugs, using a non-inferiority statistical design.93 Pazopanib was non-inferior to sunitinib (1.05, 0.90 to 1.22). Median PFS was 8.4 months with pazopanib (8.3 to 10.9) and 9.5 months with sunitinib (8.3 to 11.1), and 11 of 14 quality of life measures favored pazopanib over sunitinib.

Axitinib was approved by the FDA in January 2012 for patients with treatment refractory RCC. Approval was based on a prospective phase III study that randomized 723 previously treated patients with metastatic RCC to axitinib or sorafenib.86 Overall PFS for axitinib was 6.7 months versus 4.7 months for sorafenib (0.665, 0.544 to 0.812; one sided P<0.0001). PFS for patients who progressed on sunitinib was 4.8 months for axitinib treated patients and 3.4 months for sorafenib treated patients (0.741, 0.573.4; one sided P=0.0107).

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A subsequent randomized phase II study with 202 patients tested the hypothesis that axitinib dose escalation would improve outcomes in treatment naive patients.97 The study concluded that dose escalation improved the overall response rate but did not alter PFS. To formally test the efficacy of axitinib as a first line drug, a phase III study randomized 192 previously untreated patients with metastatic RCC to receive axitinib and 96 patients to receive sorafenib.94 PFS for axitinib was 10.1 months (7.2 to 12.1) versus 6.5 months (4.7 to 8.3) for...
sorafenib, with a stratified hazard ratio of 0.77 (0.56 to 1.05). This study failed to demonstrate the superiority of axitinib over sorafenib because of the unexpected performance of sorafenib, and because the study had an inadequate sample size.

The combination of bevacizumab plus interferon was approved by the FDA in 2009 on the basis of two prospective randomized phase III trials.82 95 In both studies this combination showed a superior PFS when compared with interferon monotherapy or interferon plus placebo. In the first study (732 patients), median PFS was 8.5 months in patients receiving bevacizumab plus interferon (7.5 to 9.7) versus 5.2 months (3.1 to 5.6) in those receiving interferon monotherapy (log rank P=0.0001). The adjusted hazard ratio was 0.71 (0.61 to 0.83; P<0.0001). In the second study, 649 patients with treatment naive metastatic RCC were randomized to bevacizumab plus interferon or placebo plus interferon. Median PFS was significantly longer in the bevacizumab plus interferon group than in the control group (10.2 vs 5.4 months; hazard ratio 0.63, 0.52 to 0.75; P<0.0001). No phase III prospective studies to test the efficacy of bevacizumab monotherapy have been published or are planned.

Although PFS endpoints were met in many of these studies, overall survival was not significantly longer in the experimental arms of any of them.100-104 This has been explained by the fact that crossover to an experimental arm or to an equivalent agent was possible in many of the patients. Where crossover was not possible and no second line drug was available, a clear survival advantage was reported in patients treated with sunitinib compared with those who received interferon.100

**mTOR inhibitors**

The second major class of molecularly targeted agents used to treat metastatic RCC targets mTOR, a serine-threonine protein kinase within the family of phosphatidylinositol-3 kinase (PI3K) related kinases. Mutations in the PI3K pathway upstream of mTOR and in mTOR itself occur in RCC,105 suggesting that this pathway is important for renal carcinogenesis. Both agents bind to the prolyl isomerase FKBP12, and this complex in turn inhibits mTOR activity.

Temsirolimus was approved by the FDA for the treatment of advanced RCC in 2007, on the basis of a prospective phase III study that randomized 626 patients with metastatic RCC and at least three poor risk features (the five MSKCC factors plus metastasis in more than one organ) to temsirolimus, an attenuated dose of temsirolimus plus interferon, or interferon monotherapy.96 These patients were different from those in previously described studies in that 20% of patients had non-clear cell histology, and only two thirds had undergone cytoreductive nephrectomy. This trial also used overall survival as a primary endpoint. Overall survival for patients treated with temsirolimus was 10.9 months versus 7.3 months for the interferon monotherapy arm (0.73, 0.58 to 0.92; P<0.008). Temsirolimus is currently used mainly in poor risk patients as a first line drug.

In a recent study that tested the utility of temsirolimus in patients who had not responded to sunitinib,97 512 patients were randomized between temsirolimus and sorafenib, with a primary PFS endpoint. No significant difference was seen for PFS (stratified hazard ratio 0.87, 0.71 to 1.07; two sided P=0.19) or overall response rate. Median PFS was 4.3 and 3.9 months in the temsirolimus and sorafenib arms, respectively. Surprisingly, overall survival was significantly longer in the sorafenib treated group than in the temsirolimus treated group (16.6 vs 12.3 months; 1.31, 1.05 to 1.63; two sided P=0.01). Reasons for this difference were not immediately apparent, but this result dampened enthusiasm for temsirolimus as a treatment for patients who do not respond to VEGF receptor inhibitors.

Everolimus was approved by the FDA in 2009 for the treatment of patients who progressed on sorafenib, sunitinib, or both. The approval was based on a phase III study that randomized 410 patients who had previously not responded to antiangiogenic therapy to everolimus or placebo.98 PFS was 4.0 months for everolimus treated patients versus 1.9 months for the placebo group (0.30, 0.22 to 0.40; P<0.0001). Everolimus is commonly used as a second line or third line drug. Currently, no data support the use of everolimus as a first line drug.

**Emerging treatments and concepts in RCC**

**Immune checkpoint blocking agents**

Recently, monoclonal antibodies against immune checkpoint blockade molecules including CTLA-4 (cytotoxic T lymphocyte antigen 4) and PD-1 (programmed cell death
1) have been shown to have clinical activity against several cancers, including RCC. For T cells to be activated for tumor cell killing, two sets of stimulating signals must be present. The first activating signal is provided by interaction between the T cell receptor and antigen bound to the major histocompatibility complex (MHC). The second signal is mediated by interaction between a T cell costimulatory molecule CD28 and its ligands, the B7 proteins.\textsuperscript{106}

CTLA-4 is expressed by activated CD4 and CD8 T cells. It is a homolog of the T cell costimulatory molecule CD28 but has a higher binding affinity for CD80 ligands. Upon T cell activation, signaling pathways lead to production of CTLA-4, which is then mobilized from intracellular vesicles to the cell surface, where it outcompetes CD28 for binding to B7 proteins. Binding of CTLA-4 to B7 proteins interrupts CD28 costimulatory signals and thereby limits T cell responses.\textsuperscript{106, 107}

Owing to the negative regulatory effects of CTLA-4 on T cell responses, it was hypothesized that blockade of CTLA-4 signaling would potentiate immune responses against tumor cells. The first antibody to block CTLA-4 (ipilimumab) was tested for the treatment of metastatic RCC in the phase II clinical trial MDX010-11 but showed only modest activity.\textsuperscript{108}

Similar to CTLA-4, PD-1 also negatively regulates T cells. It exerts this effect by binding to two ligands, PD-L1 and PD-L2, which are expressed on several cells, including antigen presenting cells and tumor cells. A recent phase I clinical trial with an anti-PD1 antibody (BMS-936558) showed an 18-28% objective response rate in patients with advanced non-small cell lung cancer, RCC, and melanoma.\textsuperscript{109} Among patients with metastatic RCC in this trial, there was a 27% clinical response rate, with most responses lasting more than a year.

Another almost concurrent phase I trial with an anti-PD-L1 antibody found an objective response rate of 6-17% in patients with advanced non-small cell lung cancer, melanoma, and RCC.\textsuperscript{110} Among patients with metastatic RCC in this trial, there was a 12% response rate, and 41% of patients whose disease stabilized remained stable for at least six months.

A phase III clinical trial of anti-PD1 in patients with metastatic RCC is ongoing. Combinations of anti-CTLA-4 and agents that target the VEGF pathway are also being investigated. However, despite their promising efficacy, immune checkpoint blocking agents have associated toxicities, known as immune related adverse events, including colitis, hepatitis, and hypopituitarism. Understanding the mechanisms and management of these adverse events will be an important aspect of effective use of these agents.

Other targeted agents

Newer agents that target the VEGF pathway, PI3K pathway, and mTOR pathway are in development. Recently, the FDA rejected a newer VEGF receptor inhibitor, tivozanib, because phase III data showed that it did not significantly improve median overall survival, although it did significantly prolong median PFS, when compared with sorafenib in patients with advanced RCC.\textsuperscript{111} Cabozantinib, a tyrosine kinase inhibitor of VEGF, the cellular receptor KIT, and MET, was tested in a phase II trial and showed a 28% overall response rate and 52% stable disease rate, with a median PFS of 14.7 months.\textsuperscript{112} A phase III clinical trial (NCT01865747) is currently evaluating the efficacy of cabozantinib versus everolimus in patients with metastatic RCC whose disease progressed after treatment with at least one tyrosine kinase inhibitor. A phase III clinical trial of dovitinib, an inhibitor of fibroblast growth factor, in addition to a VEGF receptor inhibitor, failed to show a superiority of this combination versus sorafenib in terms of PFS.\textsuperscript{113}

Similarly, several newer PI3K and mTOR inhibitors are also being developed for RCC. Among these, AZD8055 has been reported to have promising activity in preclinical studies,\textsuperscript{114} and phase I clinical trials are now complete.\textsuperscript{115} To build on the success of individual PI3K inhibitors and mTOR inhibitors, a dual inhibitor of PI3K and mTOR (NVP-BEZ235) has been developed. Preclinical studies indicated that NVP-BEZ235 had better in vitro antiproliferative effects than rapamycin.\textsuperscript{116} Currently, NVP-BEZ235 is being tested on RCC in phase I-II clinical trials (NCT01653595).

Genomic heterogeneity and impact on treatment

Owing to its prevalence, clear cell RCC is the most genetically well studied subtype of RCC. A recent analysis of data from the Cancer Genome Atlas (TCGA)—which included comprehensive integrated analyses of somatic alterations as well as analysis of DNA methylation profiles, RNA expression profiles, and protein expression profiles—has illustrated the genomic heterogeneity of clear cell RCC.\textsuperscript{13}

Firstly, these analyses confirmed previously identified major genetic changes that underlie clear cell RCC, including mutations in genes that control cellular oxygen sensing (such as \textit{VHL}) and the maintenance of chromatin states (such as \textit{PBRM1}, \textit{BAP1}, and \textit{SETD2}), as well as genes in the mTOR pathway (\textit{PIK3CA} and \textit{MTOR}).\textsuperscript{105} In addition, hypermethylation of promoter DNA was associated with higher stages and grades of clear cell RCC.

Furthermore, clear cell RCC can be separated into different prognostic groups on the basis of gene expression, DNA methylation, and protein expression profiles. Aggressive cancers with worse survival show gene expression changes that favor a metabolic shift toward fatty acid synthesis (Warburg-like phenotype). For example, reduced expression of the Krebs cycle gene \textit{AMP activated kinase (AMPK)} and increased expression of the pentose phosphate pathway gene \textit{acetyl-CoA carboxylase (ACC)} is associated with worse survival. In addition, decreased methylation of the \textit{MIR21} gene promoter correlated with increased expression of the microR-21 gene, which downregulates the tumor suppressor gene \textit{PTEN}, and is associated with worse survival. By contrast, better survival is associated with decreased methylation of the tumor suppressor gene \textit{GRB10} (growth factor receptor bound protein 10) gene promoter and increased expression of the \textit{GRB10} protein, which is a negative regulator of PI3K.

Collectively, these data suggest that key genes involved in DNA methylation, chromatin structure, and cellular metabolism may serve not only as potential prognostic markers but also as potential therapeutic targets for clear cell RCC. In addition, these observations define a great deal of genomic variety across tumors. A recent study that examined the intratumoral heterogeneity of clear cell RCC.
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GUIDELINES
European Association of Urology guidance can be found at: www.uroweb.org/gls/pdf/10_Renal_Cell_Carcinoma_LR.pdf

The National Comprehensive Cancer Network provides regularly updated cancer treatment guidelines and maintains a set of guidelines for renal cell carcinoma, which can be accessed at: www.nccn.org/professionals/physician_gls/f_guidelines.asp

FUTURE RESEARCH QUESTIONS
What are the key genomic features that define a lethal renal cell carcinoma?
Does a risk adapted strategy for follow-up affect the natural course of disease?
How does resistance to antiangiogenic therapy develop and how can we overcome this resistance?
Which patients are most likely to benefit from checkpoint blocking antibodies and other classes of biological agents?
How can we rationally target drivers of non-clear cell renal cell carcinoma?

identified substantial differences in mutations from different sites within a single primary tumor, as well as a distinct mutational profile for metastatic lesions. The mutations identified also showed evidence of convergent evolution.

Further studies will be needed to translate these findings into clinical settings.

Conclusion
RCC is an important and increasing public health threat in the developed world. Substantial progress has been made in the management of localized disease, with nephron sparing approaches emerging in the past 15 years. For patients with metastatic disease, cytoreductive nephrectomy is still considered a reasonable approach in those who subsequently receive contemporary systemic drugs. The most commonly used agents to treat metastatic RCC are drugs that inhibit VEGF receptors, such as sunitinib and pazopanib, and those that inhibit mTOR, such as everolimus and temsirolimus. Unfortunately, most patients ultimately progress on treatment and die of their disease.

The new class of checkpoint blocking antibodies that target the PD-1 and the CTLA-4 receptors may provide profound and durable responses in a subset of patients. Ongoing work will help define the utility of these agents in the treatment of RCC, and will enable us to identify those most likely to benefit. Similar efforts are under way to identify the determinants of response and resistance to antiangiogenic drugs, and to design the next generation of agents, which will target factors that engender resistance to established agents.

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