New Treatment Paradigms in Renal Cell Carcinoma

Edited by

Ronald M. Bukowski, MD
Director of Experimental Therapeutics
Cleveland Clinic Taussig Cancer Center
Professor of Medicine
The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Cleveland, Ohio
Clinical Oncology Advisory Board

Note to the reader
The information in this book has been carefully reviewed for accuracy of dosage and indications. Before prescribing any drug, however, the clinician should consult the manufacturer's current package labeling for accepted indications, absolute dosage recommendations, and other information pertinent to the safe and effective use of the product described. This is especially important when drugs are given in combination or as an adjunct to other forms of therapy. Furthermore, some of the medications described herein, as well as some of the indications mentioned, may not have been approved by the U.S. Food and Drug administration at the time of publication. This possibility should be borne in mind before prescribing or recommending any drug or regimen.

Educational activities in the form of monographs, audio programs, supplements, and other formats are sent to the readership of ONCOLOGY and Oncology News International on a regular basis. All recipients of the journals can opt out of receiving them and accompanying educational activities at any time by contacting our circulation department at CMPMedica, phone: (203) 662-6551 or by e-mail: wdingle@cmp.com.

Copyright ©2007 by CMP Healthcare Media, LLC. All rights reserved. This book is protected by copyright. No part of it may be reproduced in any manner or by any means, electronic or mechanical, without the written permission of the publisher.

Library of Congress Catalog Card Number 2007929230

ISBN 9781891483530

Single copies of this book are available for $19.95 each. For information on obtaining additional copies, contact the publisher, CMPMedica, The Oncology Group, 600 Community Drive, Manhasset, New York 11030. Telephone (212) 600-3012, Fax (212) 600-3050.

Cover image description: Death of a tumor after effective anti-angiogenic therapy, static “time lapse” rendering. The treatment causes new tumor vasculature (angiogenesis) to collapse and retreat. The tumor is shown changing from robust (upper left corner) to anoxic and dying (lower right corner). Tumor necrosis occurs from the inside out. Credit: Illustration by XVIVO LLC/PhototakeUSA.com
Contents

Contributing Authors iv

Continuing Medical Education vii

1 Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment
   Vitaly Margulis, MD, and Christopher G. Wood, MD, FACS 1

2 Renal Cell Carcinoma: Pathologic and Molecular Characteristics
   Ming Zhou, MD, PhD 19

3 Prognostic Factors in Renal Cell Carcinoma Patients: Localized and
   Metastatic Disease
   Sumanta K. Pal, MD, and Robert A. Figlin, MD, FACP 35

4 Advanced Clear Cell Carcinoma: Immunologic Characteristics and Results
   with Vaccines and Cytokines
   Guru Sonpavde, MD, and Thomas E. Hutson, DO, PharmD, FACP 61

5 Multi-Targeted Kinase Inhibitors: New Treatment Paradigms for Advanced
   Clear Cell Carcinoma
   Sabry George, MD, and Ronald M. Bukowski, MD 73

6 Novel Strategies in the Management of Advanced Renal Cell Carcinoma
   Jorge A. Garcia, MD 95

7 Adjuvant and Neoadjuvant Therapy for Renal Cell Carcinoma: Past and
   Future Strategies
   David A. Kunkle, MD, and Robert G. Uzzo, MD 115

CME Post-Test 137

Index 141

To earn CME credit, go to www.cancernetwork.com/cme
Contributing Authors

Ronald M. Bukowski, MD  
Director of Experimental Therapeutics  
Cleveland Clinic Taussig Cancer Center  
Professor of Medicine  
The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
Cleveland, Ohio

Robert A. Figlin, MD, FACP  
Associate Director for Clinical Research, Comprehensive Cancer Center  
Chair, Division of Medical Oncology and Therapeutics Research  
Arthur and Rosalie Kaplan Professor of Medical Oncology  
City of Hope National Medical Center  
Duarte, California

Jorge A. Garcia, MD  
Associate Staff  
Departments of Solid Tumor Oncology and Urology  
Cleveland Clinic Taussig Cancer Institute  
Glickman Urological and Kidney Institute  
Assistant Professor of Medicine  
The Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
Cleveland, Ohio

Saby George, MD  
Clinical Research Fellow  
Department of Hematology and Medical Oncology  
Experimental Therapeutics  
Cleveland Clinic Taussig Cancer Center  
The Cleveland Clinic Foundation  
Cleveland, Ohio
Thomas E. Hutson, DO, PharmD, FACP
Director, Genitourinary Oncology Program
Texas Oncology, PA
Baylor Charles A. Sammons Cancer Center
Dallas, Texas

David A. Kunkle, MD
Chief Resident
Department of Urologic Oncology
Fox Chase Cancer Center
Temple University School of Medicine
Philadelphia, Pennsylvania

Vitaly Margulis, MD
Fellow, Urologic Oncology
Department of Urology
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Sumanta K. Pal, MD
Division of Medical Oncology and Therapeutics Research
City of Hope National Medical Center
Duarte, California

Guru Sonpavde, MD
Genitourinary Oncology Program
Texas Oncology and U.S. Oncology Research
Clinical Assistant Professor, Oncology and Urology
Baylor College of Medicine and University of Texas
Houston, Texas

Robert G. Uzzo, MD, FACS
Associate Professor
Department of Urologic Oncology
Fox Chase Cancer Center
Temple University School of Medicine
Philadelphia, Pennsylvania

Christopher G. Wood, MD, FACS
Associate Professor of Urology
Department of Urology
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Continued
Ming Zhou, MD, PhD
Staff Pathologist
Director, Tissue Microarray Core, MMP Laboratory
Departments of Anatomic Pathology
Cancer Biology
Glickman Urological and Kidney Institute
Cleveland Clinic Taussig Cancer Center
Cleveland, Ohio
Continuing Medical Education

Monograph

Activity Release Date: November 1, 2007
Activity Expiration Date: November 1, 2008

About the Activity

The CME activity is based on the information learned from reading this monograph, *New Treatment Paradigms in Renal Cell Carcinoma*. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology.

This activity has been developed and approved under the direction of Beam Institute.

Activity Learning Objectives

After reading *New Treatment Paradigms in Renal Cell Carcinoma*, participants should be able to:

- Demonstrate an understanding of the molecular characteristics of renal cell carcinoma and how targeted therapies work on a molecular basis to affect renal cell carcinoma.
- Incorporate molecular treatments into everyday practice.
- Demonstrate knowledge of the latest novel strategies in targeted therapeutic approaches to renal cell carcinoma.

Target Audience

This activity targets physicians in the fields of oncology and hematology.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Beam Institute and The Oncology Group. Beam Institute is accredited by the ACCME to provide continuing medical education for physicians.
Credit Designation

Beam Institute designates this educational activity for a maximum of 3 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Physicians not licensed in the United States who participate in this CME activity are eligible for AMA PRA Category 1 Credit(s)™.

Compliance Statement

This activity is an independent educational activity under the direction of Beam Institute. The activity was planned and implemented in accordance with the Essential Areas and policies of the ACCME, the Ethical Opinions/Guidelines of the AMA, the FDA, the OIG, and the PhRMA Code on Interactions with Healthcare Professionals, thus assuring the highest degree of independence, fair balance, scientific rigor, and objectivity. However, Beam Institute, the Grantor, and CMPMedica shall in no way be liable for the currency of information or for any errors, omissions, or inaccuracies in the activity. Discussions concerning drugs, dosages, and procedures may reflect the clinical experience of the author(s), or they may be derived from the professional literature or other sources and may suggest uses that are investigational in nature and are not approved labeling or indications. Activity participants are encouraged to refer to primary references or to the full prescribing information resources. The opinions and recommendations presented herein are those of the author(s) and do not necessarily reflect the views of the provider or producer.

Financial Disclosure

Dr. Bukowski is a member of the speakers’ bureau and receives research support from Bayer, Pfizer, and Wyeth. He also receives research support and serves on the advisory board for Bristol–Meyers Squibb, Genentech, Novartis, and Sanofi–Aventis. Dr. Figlin receives research support from GlaxoSmithKline, Pfizer, Novartis, and Wyeth; and serves as a consultant for Bayer, Pfizer, Novartis, and Wyeth. Dr. Garcia is a member of the speakers’ bureau and receives research support from Pfizer; he also serves on the advisory board for Wyeth and receives research support from Celgene and Novartis. Dr. Hutson is a consultant and a member of the speakers’ bureau for Bayer/Onyx and Pfizer; he receives research support from Alaxo and Wyeth. Dr. Sonpavde receives research support from Pfizer. Dr. Uzzo is a member of the speakers’ bureau for Bayer/Onyx. Dr. Wood is a member of the speakers’ bureau and serves on the advisory board for Pfizer. Dr. Kunkle, Dr. Margulis, Dr. Pal, and Dr. Zhou indicated they have no financial interest or other relationship with the manufacturers of any products or providers of any services mentioned in this book.

To earn CME credit, go to www.cancernetwork.com/cme
Copyright

Copyrights owned by Beam Institute, a division of CME LLC. Copyright ©2007.

Contact Information

We would like to hear your comments regarding this or other activities provided by Beam Institute. In addition, suggestions for future programming are welcome. Contact us at:

Address: Director of Continuing Education  
Beam Institute  
CME LLC  
11 West 19th Street, 3rd Floor  
New York, NY 10011-4280  
Phone: 888-618-5781  
Fax: 212-600-3050  
E-mail: beaminstitute@cmp.com

Supported by an educational grant from
Arguably the most lethal of urologic cancers, renal cell carcinoma (RCC) represents a growing health problem in the United States and around the world. The American Cancer Society estimates that 51,190 people in the United States will present with kidney cancer and 12,890 will die from the disease in 2007 (1). The growing incidence of kidney cancer is in part due to the detection of asymptomatic renal masses found serendipitously through the increased use of abdominal imaging for nonspecific complaints, but also to a real rise in the incidence of the disease as a consequence of increased penetration of as yet incompletely elucidated genetic and epigenetic influences (2).

Epidemiologic studies have linked a variety of factors to the genesis of renal malignancy, including smoking, obesity, hypertension, diabetes mellitus, and a variety of dietary influences and environmental exposures (3). Most of these studies suffer from the presence of confounding variables that make definitive conclusions about the true causes of sporadic RCC difficult. The study of inheritable forms of kidney cancer has provided valuable insight into the genetic basis of renal malignancy, with the identification of specific genetic mutations that correlate with the genesis of cancer (4). These discoveries, in turn, have led to the development of many therapeutic interventions that target specific molecular pathways important in kidney cancer, resulting in improved disease response and outcomes. What is becoming increasingly apparent, however, is that RCC is a heterogeneous collection of diseases with diverse genetic alterations more complex than those elucidated in the study of inherited kidney cancer. The c-met proto-oncogene, for example, contains an activating mutation that leads to certain heritable subtypes of papillary renal cell cancer, but it is mutated in only approximately 10% of patients with sporadic, non-inherited renal cell carcinoma.
forms of the disease (5). More research is necessary to identify relevant therapeutic targets to make further inroads into the successful treatment of advanced disease and perhaps provide insight into the development of successful adjuvant and chemopreventive strategies.

Surgery is a mainstay in the successful treatment of kidney cancer in all stages of disease. Curative when applied in the localized or locally advanced setting, surgical control of the primary tumor has also been shown to be a critical part of the multidisciplinary approach to patients with metastatic RCC. Current efforts have been focused on the development and implementation of minimally invasive and non-invasive techniques to control primary renal tumors, in a manner that maintains oncologic equipoise with open surgical approaches. In this chapter, we outline approaches to the diagnosis and staging of RCC and then focus on the role of surgery in the management of this disease.

Diagnosis and Staging

Clinical Features

Recent clinical surveys have revealed that the incidental detection of RCC is rising, partly because of increased use of imaging procedures such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) (3). These changes resulted in a stage migration, contributed to improved oncologic outcomes, and led to an evolution in the surgical management of RCC (6).

Although patients with RCC can present with a wide array of symptoms or laboratory abnormalities, or both, the majority of patients diagnosed today are asymptomatic. The classic triad of RCC (flank pain, hematuria, and a palpable abdominal renal mass) occurs in less than 10% of current patients. Other symptoms and signs are related to the invasion of the venous system by the tumor thrombus, infiltration or compression of adjacent organs by a growing renal mass, or the presence of distant metastases (7,8).

Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCC, and in some instances may be due to ectopic production of various hormones such as erythropoietin, parathyroid hormone–related protein, gonadotropins, renin, glucagon, and insulin. The most common paraneoplastic syndromes are hypertension, cachexia, and weight loss (7,8). Table 1 summarizes the signs, symptoms, and paraneoplastic syndromes frequently associated with RCC. In addition to providing important diagnostic information, an assessment of RCC-associated symptoms yields important prognostic information. As discussed in the subsequent section, several clinical series clearly document improved cancer-specific survival rates among patients who are diagnosed incidentally, compared to those patients who present with symptoms attributable to RCC (9,10).
Clinical and Radiologic Evaluation

Physical examination plays a limited role in the diagnosis of RCC, but it may provide important information regarding the anatomic extent of the disease. The presence of a non-reducing varicocele or bilateral lower extremity edema suggests the presence of venous involvement, while palpable lymphadenopathy suggests metastatic dissemination (7,8).

Laboratory evaluation centers on an assessment of global renal function and screening for the presence of subclinical metastatic disease or associated paraneoplastic syndromes. The most common laboratory measurements are serum creatinine, hemoglobin, alkaline phosphatase, and hepatic function tests (7,8).

A dedicated (thin-slice) renal CT scan with and without contrast remains the single most important radiographic test for determining the nature of a renal mass. It serves to verify the diagnosis and local extent of RCC and provides radiologic and functional assessment of the contralateral kidney and adrenal gland while simultaneously evaluating for the presence of intra-abdominal metastatic disease (11,12). Plain chest radiography is routinely used to detect pulmonary metastases, but chest CT is advocated in patients at high risk for harboring metastatic RCC (7,8).

The advent of real-time and gray-scale ultrasonography has improved the ability of sonar techniques to distinguish homogeneous (sonolucent) from heterogeneous lesions with internal echoes. Consequently, ultrasonographic renal evaluation is particularly useful in differentiating between a simple benign cyst and a more complex cyst or a solid tumor (11,12).

MRI is a study of choice in patients with suspected venous involvement, renal insufficiency, or allergy to intravenous contrast (11,12). Renal arteriography is usually used
only in selected cases in which preoperative mapping of vasculature is necessary, such as when nephron-sparing surgery is contemplated. Likewise, radiologic bone and brain imaging is performed if indicated by clinical or laboratory findings (7,8).

In the era of targeted therapies for RCC, assessment of tumor vascularization may provide important prognostic information and be used to evaluate response to treatment. Doppler ultrasonography with contrast agent injection is a promising new modality, which has been shown to provide both morphologic and functional information regarding tumor vascularity (12).

18F fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of cancer is based on the observation that many malignant tumors are characterized by accelerated glucose use when compared with surrounding normal tissues. FDG-PET has been applied for the diagnosis, staging, and follow-up, and for monitoring response to therapy for several cancers (11,12). In patients with RCC, FDG-PET does not adequately characterize small metastatic lesions, but has been demonstrated to be predictive for the presence of RCC in lesions imaged (11,12). To date, the role of FDG-PET in the staging and detection of distant metastases from RCC has not been clearly established; however, the evolution of PET technology in the future may complement anatomic radiologic imaging modalities and may alleviate the need for tissue biopsy.

Percutaneous Renal Biopsy

Due to concerns about safety and accuracy, the role for percutaneous biopsy of renal masses has been limited in the past. However, with the development of new biopsy techniques and wider experience with percutaneous energy ablation therapies, needle core biopsy with or without fine-needle aspiration has been shown to provide adequate specimens for an accurate diagnosis in more than 90% of renal masses (13,14). Moreover, concerns about the safety of percutaneous renal biopsy are not justified, as the risk of post-biopsy tumor seeding or significant bleeding is exceedingly low (13,14). With additional experience and longer follow-up, percutaneous renal biopsy has the potential to decrease unnecessary treatment of benign renal masses, which are present in up to a third of patients, and may allow for an improved selection of renal tumors for active surveillance and minimally invasive ablative therapies. In the future, renal tissue obtained from percutaneous biopsy may be used for molecular tumor characterization and to facilitate subsequent delivery of patient-specific targeted therapy.

Staging

An accurate and clinically useful staging system is an essential tool. It is used to provide patients with counseling regarding prognosis, select treatment modalities, and determine eligibility for clinical trials. Tumor stage, as determined by the American Joint Committee
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

on Cancer primary tumor classification system (Table 2), remains the most important and widely utilized predictor of progression-free and overall survival after surgical management of RCC (15). Recent literature reveals that 5-year cancer-specific survival after radical nephrectomy (RN) ranges from 75% to 95% for patients with organ-confined disease to 0%–5% for patients with metastatic disease at presentation (16,17). Based on peer-reviewed observations in the literature, and reflecting changing trends in RCC presenta-

Table 2. The American Joint Committee on Cancer 2002 staging system for renal cell carcinoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3a</td>
</tr>
<tr>
<td>T3b</td>
</tr>
<tr>
<td>T3c</td>
</tr>
<tr>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

In recent years, the American Joint Committee on Cancer tumor, node, metastasis (TNM) staging system has been continuously modified to improve its accuracy. The optimal risk stratification of RCC patients within the current TNM staging system is still debated, however, despite all the implemented and proposed modifications.

Currently, controversy exists regarding the prognostic significance of tumor size, ipsilateral adrenal invasion, location of extrarenal tumor extension and the level of venous tumor thrombus. Previously published studies have identified absolute tumor size as a critical predictive factor across the spectrum of localized and locally advanced renal tumors, and have urged various modifications to the current staging system (18). Likewise, numerous clinical series have clearly demonstrated that tumors with direct ipsilateral adrenal invasion, currently classified as T3a, should be staged as T4 because they behave more aggressively than tumors involving perinephric or renal sinus fat (19,20).

In contrast to the current TNM staging system of RCC, several investigators have demonstrated that, in a multivariate analysis, the risk of cancer recurrence and cancer-specific death in patients with RCC and venous involvement did not differ when stratified by level of the tumor thrombus (20,21). Even though it has been demonstrated that extrarenal tumor extension portends worse prognosis among patients with venous tumor thrombus, current primary tumor classification for RCC does not differentiate between patients with venous thrombus only and patients with both pathologic features (20,22).

Keeping up with the modern demand for evidence-based medical practice, and based on compelling clinical evidence, several investigators have proposed changes to the current staging system of RCC, which will be reflected in the upcoming revisions of the RCC TNM classification (20,22,23).

Despite their improved predictive ability, the purely anatomic staging systems discussed above do not incorporate alternative clinicopathologic factors, such as tumor grade, histologic subtype, presence of coagulative or gross tumor necrosis, sarcomatoid differentiation, or patient performance status, that are also important in RCC prognosis (9,18,24). Identification of novel clinicopathologic predictors in RCC has resulted in a gradual transition from the use of solitary clinical factors, such as the TNM staging system, to the introduction of systems that integrate multiple validated prognostic factors. The University of California Integrated Staging System (UISS), the Mayo Clinic stage, size, grade, and necrosis score, and the Memorial Sloan-Kettering Cancer Center RCC nomograms, discussed in Chapter 3, are some of the recently introduced integrated staging algorithms that have already been validated and integrated into clinical practice (9,18,24).

Surgical Management

Laparoscopic and Open Radical Nephrectomy

Since its pioneering description by Robson et al., surgical removal of the primary tumor with RN has remained the mainstay of treatment for patients with RCC (25). Although
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

basic surgical and oncologic principles established by Robson remain unchanged, the modern surgical armamentarium for treatment of RCC has expanded with the evolution of standard open, minimally invasive, and nephron-sparing techniques. The basic principles of this procedure include early ligation of the renal vasculature, en bloc removal of the kidney and adrenal gland within the surrounding perinephric fat and Gerota’s fascia, and an extensive lymph node dissection, assuring negative surgical margins while minimizing vascular and intraperitoneal dissemination of cancer cells (25). The oncologic efficacy of RN has been confirmed in multiple large series, which document 5-year survival rates after RN that range from 95% to 75% for patients with organ-confined disease to 80%–40% for patients with locally advanced RCC (16).

Since the initial description of laparoscopic nephrectomy (LRN) in 1991, LRN has emerged as an equally efficacious and minimally morbid surgical alternative to open RN in the management of low-volume, localized RCC (26). Compared with open surgery, patients benefit from shorter hospitalization, more rapid convalescence, decreased pain, and improved cosmesis. Although no randomized prospective studies comparing RN and LRN exist, multiple retrospective series have confirmed the similar long-term oncologic efficacy of LRN and open surgery (26). Increasing experience with LRN, traditionally reserved for patients with organ-confined renal tumors, has led to its use at specialized surgical centers in patients with locally advanced RCC or as cytoreductive surgery in patients with distant metastatic disease (27).

Role of Routine Adrenalectomy and Lymph Node Dissection

The original description of RN by Robson included routine removal of the ipsilateral adrenal gland and extensive lymph node dissection (LND) of the paraaortic and paracaval lymph nodes from the crus of the diaphragm to the bifurcation of the aorta (25). The applicability of this dictum, written in the era of poor preoperative imaging and a high proportion of advanced disease at presentation, has been questioned in the modern era of small incidentally discovered RCC and sophisticated radiologic staging modalities. Several reports have documented the relative rarity of isolated ipsilateral adrenal metastases or direct adrenal invasion by RCC in contemporary patient cohorts. Specifically, in patients without evidence of systemic metastatic disease, presence of adrenal involvement by RCC has been demonstrated in only 1%–5% of cases (28,29). Current imaging modalities such as CT and MRI have demonstrated greater than 99% specificity and nearly 90% sensitivity in detecting adrenal involvement preoperatively (28,29). Moreover, several retrospective series failed to demonstrate a survival benefit to routine adrenalectomy in addition to RN (28,30). Available evidence suggests that adrenalectomy should be performed only if adrenal involvement is suspected on preoperative imaging or during surgical exploration at the time of RN.

Similarly, the need for routine LND during RN for the treatment of RCC remains controversial. The reported incidence of locoregional lymph node metastasis associated
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

with RCC varies significantly throughout the modern literature, but largely depends on the primary tumor stage, presence of associated lymphadenopathy, and the extent of the lymphadenectomy performed (31). Up to 45% of patients with locally advanced RCC have been found to have malignant lymph node deposits, compared to 5% of patients with organ-confined disease (31–33). Moreover, the use of advanced imaging techniques has made the discovery of unsuspected nodal involvement in patients with no radiologic or clinical evidence of lymphadenopathy extremely rare (1%–3%) (32).

The only randomized prospective clinical study to evaluate the role of routine LND at the time of RN for RCC (European Organisation for Research and Treatment of Cancer [EORTC] 30881) has not reached maturity, but preliminary results failed to demonstrate any survival advantage with routine LND (32). Because only 3% of patients who underwent LND at the time of RN had lymph node metastases and few patients progressed or died from RCC, it is difficult to draw conclusions about the therapeutic efficacy of LND.

In contrast, several recent reports presented more convincing evidence supporting the therapeutic efficacy of LND in patients with clinically positive lymph nodes. Numerous single-center reports have established that patients with suspected lymph node involvement at the time of RN who underwent LND had significantly longer survival than node-positive patients whose nodal tissue was left in situ (34,35). Although retrospective in nature, these studies suggest that the biology and outcomes of lymph node–positive RCC patients can be altered by surgical removal of cancerous lymph nodes, making a strong case for lymphadenectomy when nodal involvement is suspected.

In summary, patients with organ-confined RCC and no evidence of lymphadenopathy are unlikely to have associated lymph node metastasis and can be spared the potential morbidity of LND at the time of RN. Conversely, patients with locally advanced RCC and patients with a radiologic or intraoperative finding of lymphadenopathy are at increased risk of harboring metastatic lymph node deposits and should undergo LND in addition to RN.

Nephron-Sparing Surgery

Since the late 1990s, downward tumor stage migration, coupled with development of accurate pre- and intraoperative radiologic imaging and improved surgical techniques, has established nephron-sparing surgery (NSS) as a therapeutic option for all small renal masses (36). NSS, performed openly or laparoscopically, allows an oncologically complete local excision of RCC, while preserving a functional renal remnant (37).

In the era of increased incidental detection of small renal masses, organ preservation with NSS is of paramount importance in patients with RCC. First, patients with kidney cancer are at increased lifetime risk of tumor formation in the contralateral kidney. The incidence of metachronous contralateral tumor development after RN varies throughout the literature, with most reports ranging from 2% to 6% (38,39). Recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated a relatively
constant incidence of metachronous contralateral tumor development over time, continuing well beyond 10 years of follow-up (38). Additionally, recent reports clearly indicate that patients subjected to RN are at a greater risk of developing renal insufficiency as compared with matched patients treated with NSS (40).

Accordingly, the indications for NSS—initially described for the treatment of bilateral RCC or tumor in a solitary kidney—have broadened over time. Based on several large retrospective series, and, most recently, supported by a single prospective randomized controlled trial, elective NSS has been accepted as a standard therapeutic modality for organ-confined renal masses 4 cm or smaller in diameter (36,41). The seemingly arbitrary cut-off size for elective NSS has been challenged by several investigators who have demonstrated that, for all T1 (organ-confined, <7 cm) renal tumors, the risk of dying from RCC is driven by inherent tumor biology rather than surgical approach (42,43). In addition, there is emerging evidence that NSS can safely be performed for patients with locally advanced tumors, provided an adequate surgical margin and sufficient remaining renal parenchyma can be obtained (44).

Criticisms of NSS include concerns about local recurrence due to incomplete tumor resection or tumor multifocality. Several large retrospective studies document the presence of multifocal RCC in 4%–19% of kidney specimens, although the incidence of multifocality not visualized on preoperative imaging or at exploration is reported to be significantly lower, at 3%–6% (45).

**Energy-Based Tissue Ablation**

Ablative techniques offer advantages over extirpative techniques by reducing perioperative morbidity, shortening hospital stays, promoting faster recovery, and importantly, potentially treating patients who are poor surgical candidates while preserving renal parenchyma. Since the late 1990s, numerous ablative technologies have been explored, but cryoablation (CA) and radiofrequency ablation (RFA) have emerged as viable treatment alternatives for a select group of patients with localized renal tumors (46).

RFA works by transmitting a high-frequency electrical current through an electrode placed directly into the renal tumor, which causes ions in the surrounding tissues to vibrate, creating frictional heat and tissue destruction (47). In clinical practice RFA has been used percutaneously or laparoscopically in patients with small renal tumors who have renal insufficiency, multiple bilateral renal tumors, or in those who are poor surgical candidates (47). Traditionally, ultrasonography, CT, and MRI have all been used to target lesions, but with the advent of fluoroscopic CT and open MRI, real-time ablation monitoring can be achieved. In the largest series of RFA-treated tumors published to date, initial ablation was successful in 107 of the 109 tumors, with a 2.8% recurrence rate reported during a mean follow-up of 19 months (48).

CA achieves tissue destruction by two sequential synergistic mechanisms: direct cytotoxic damage by intracellular ice crystallization during the rapid freeze phase, followed
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

by an indirect ischemic injury due to obliteration of local microvasculature during the subsequent slow thaw phase (49). Although CA can be performed by open and percutaneous techniques, to date, the majority of procedures are performed using laparoscopic techniques under ultrasound monitoring. As with RFA, recent introduction of open MRI and real-time fluoroscopic CT have allowed real-time monitoring of the ice ball in a percutaneous approach (49). In the largest series of laparoscopic CA, incomplete tumor ablation or recurrence was reported in 2 of 156 patients treated (50).

In a multi-institutional review of complications after RFA and CA, complications were reported in 8.2% and 13.6% of patients, respectively. The vast majority of complications were minor, with pain and paresthesia at the site of probe insertion being most frequently reported for both techniques (51).

Criticisms of energy-based ablative techniques center on the need for histologic confirmation of the completeness of tumor destruction and lack of long-term follow-up. Because tissue is left in place after thermal ablation, cross-sectional imaging with CT or MRI is used to document lack of enhancement in the ablated tumor. Whether this actually correlates with the absence of viable cancer remains a subject of much debate (46).

In summary, RFA and CA both appear to be safe and effective methods of treating small renal tumors, and, although early oncologic results appear promising, long-term follow-up data are necessary to prove the efficacy and durability of these methods.

Newer thermal energy–based strategies, such as high-intensity focused ultrasound, laser-induced and microwave thermotherapy, and intracavitary photon radiation, hold theoretical promise, but await additional investigation before widespread deployment.

Active Surveillance

Expectant treatment, also referred to as watchful waiting or active surveillance with delayed treatment, is an accepted management modality for several urologic tumors such as testicular and prostate cancer. Recently, numerous investigators have prospectively evaluated the natural history of untreated small renal masses (52). These studies uniformly show that most small renal masses grow slowly, if at all, and that metastases are unlikely to occur before the mass shows rapid growth (52). In a meta-analysis study of 234 lesions treated with active surveillance at a median follow-up time of 32 months, average growth rate of only 0.28 cm yearly (range, 0.09–0.86) was reported (53). The same authors have also demonstrated that only 1.0% of patients (3 of 287) progressed to metastatic disease while on a surveillance protocol (53). However, conclusions from these studies are currently hindered by the lack of long-term follow-up, limited histologic information of observed tumors, and the absence of uniform surveillance strategies. Overall, active surveillance appears to be a viable and safe option for patients with excessive comorbidities and short life expectancy. Before wider application of active surveillance can be recommended, there is a clear need for prognostic markers of tumor progression and for prospective validation of follow-up schemes.
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

Risk-Based Follow-Up Strategies

Significant recent advances in the diagnosis, staging, and treatment of patients with RCC have resulted in improved survival of patients with locally recurrent and metastatic disease. In some reports, 30%–50% of patients with isolated local recurrence are found to be free of disease progression after aggressive extirpative treatment with or without adjuvant therapy (54,55). Response rates of 10%–40% have been reported after systemic therapy for patients with metastatic RCC (17). Mounting evidence indicates that success of clinical intervention for locally recurrent or metastatic RCC is inversely proportional to the disease volume at the time of salvage treatment, and timely identification of relapse after surgical extirpation is imperative in the treatment of these patients. Although no consensus on surveillance regimens for patients after surgical resection of RCC exist, the TNM classification system remains the most important prognosticator of outcome in RCC and a cornerstone of several currently proposed surveillance strategies (Table 3) (56,57).

Several novel clinical, pathologic, and molecular markers have recently been shown to correlate with clinical tumor behavior and predict disease recurrence independent of tumor stage (58). Integrated staging algorithms, such as the University of California Integrated Staging System, rely on a combined and structured analysis of clinical information, anatomic extent of the disease, and histopathologic criteria to determine the optimal individual surveillance strategy (see Table 3) (59). In the future, integration of molecular markers of disease progression into recurrence prediction algorithms should revolutionize surveillance protocols for RCC by tailoring follow-up to specific molecular classifications.

Role of Surgery in the Setting of Metastatic Renal Cell Carcinoma

Unlike the management of most other advanced solid tumor malignancies, surgical management of the primary tumor in the setting of metastatic RCC remains a cornerstone of the multidisciplinary approach to patient care.

Before 2001, the virtues of cytoreductive nephrectomy were championed in the literature primarily by single-institution retrospective series that demonstrated reasonable safety, with a majority of patients going on to receive systemic therapy after recovering from surgery (60). Advocates of initial cytoreductive nephrectomy noted that the primary tumor rarely responded to systemic immunotherapy and that surgical debulking of the primary tumor may have improved response to therapy and survival. Critics argued that surgical morbidity or postoperative disease progression may preclude patients from receiving the systemic therapy necessary to treat their metastatic disease. The group at Tufts University used their retrospective analysis to identify specific patient selection criteria that resulted in improved outcome with initial surgery (61). These criteria included the presence of predominant clear cell histology; good perfor-
### Table 3. Surveillance guidelines after therapy for clinically localized renal cell carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>History evaluation, physical exam, and laboratory</th>
<th>Chest imaging</th>
<th>Abdominal imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical nephrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>q1yr</td>
<td>q1yr</td>
<td>None</td>
</tr>
<tr>
<td>T2</td>
<td>q6mo x 3 yr, then q1yr</td>
<td>q6mo x 3 yr, then q1yr</td>
<td>At 24 mo, at 60 mo</td>
</tr>
<tr>
<td>T3</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 24 mo, at 60 mo</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>q1yr</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>T2</td>
<td>q1yr</td>
<td>q1yr</td>
<td>At 24 mo, then q2yr</td>
</tr>
<tr>
<td>T3</td>
<td>q6mo</td>
<td>q6mo</td>
<td>At 12 mo, then q2yr</td>
</tr>
<tr>
<td>Umeå University</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>None</td>
</tr>
<tr>
<td>T2</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 6 mo, at 12 mo</td>
</tr>
<tr>
<td>T3</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 3 mo, q6mo x 3 yr, then q1yr</td>
<td>At 6 mo, at 12 mo</td>
</tr>
<tr>
<td>University of California, Los Angeles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR</td>
<td>q1yr x 5 yr</td>
<td>q1yr x 5 yr</td>
<td>At 2 yr, at 4 yr</td>
</tr>
<tr>
<td>IR</td>
<td>q6mo x 5 yr, then q2yr</td>
<td>q6mo x 5 yr, then q2yr</td>
<td>At 1 yr, then q2yr</td>
</tr>
<tr>
<td>HR</td>
<td>q6mo x 5 yr, then q2yr</td>
<td>q6mo x 5 yr, then q2yr</td>
<td>q6mo x 2 yr, then q1yr</td>
</tr>
<tr>
<td>LN+</td>
<td>At 3 mo, q6mo x 2 yr, then q1yr</td>
<td>At 3 mo, q6mo x 2 yr, then q1yr</td>
<td>At 3 mo, q6mo x 2 yr, then q1yr</td>
</tr>
</tbody>
</table>

| Partial nephrectomy | | | |
| Cleveland Clinic | | | |
| T1 | q1yr | None | None |
| T2 | q1yr | q1yr | At 24 mo, then q2yr |
| T3 | q6mo | q6mo | q6mo x 3 yr, then q1yr |

(continued)
Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

Table 3. Surveillance guidelines after therapy for clinically localized renal cell carcinoma (Continued)

<table>
<thead>
<tr>
<th>Stage</th>
<th>History evaluation, physical exam, and laboratory</th>
<th>Chest imaging</th>
<th>Abdominal imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matin et al.</td>
<td>T1, q1yr, q1yr</td>
<td>q1yr, q1yr</td>
<td>At 1, 3, 6, 12 mo, then q1yr</td>
</tr>
</tbody>
</table>

*Energy ablation*

- 2002 American Joint Committee on Cancer tumor, node, metastasis staging of renal cell carcinoma.
- Complete blood cell count, serum chemistries, and liver function tests.
- Chest x-ray; UCLA protocol—chest computed tomography, alternating with chest x-ray.
- Abdominal magnetic resonance imaging if abdominal computed tomography clinically contraindicated.
- No follow-up recommended if tumor < 5 cm or diploid.

Performance status; absence of liver, central nervous system, or extensive bone metastases; and the ability to resect at least 75% of the tumor burden at the time of surgery. In applying these criteria, the authors reported that 93% of patients recovered and went on to receive interleukin-2–based systemic immunotherapy, with a response rate of 39% and a median survival of 20.5 months (61). The results of two phase III randomized trials, Southwest Oncology Group (SWOG) 8949 and EORTC 30947, were reported in 2001, both demonstrating that cytoreductive nephrectomy in combination with interferon therapy improved survival over interferon therapy alone, thus solidifying initial cytoreductive surgery as a mainstay of treatment in properly selected patients (62). Since that time, upfront cytoreductive surgery has become the standard of care in the management of patients with metastatic RCC with clear cell histology. Its role in the management of metastatic RCC with non–clear cell histology remains unknown and unproven, as these patients have an overall poor prognosis in large part due to lack of response to existing systemic therapies (63).

The development, clinical testing, and government approval of targeted therapies, such as sunitinib, sorafenib, and temsirolimus, have dramatically improved the outlook for patients with metastatic disease, demonstrating significant delays in time to disease progression, improved disease response, and, in some cases, improved survival over traditional systemic immunotherapies (64). For the first time, in the limited number of patients who have been treated with their primary tumor in place, disease response in the primary tumor, in addition to metastatic sites, has been recognized. As a consequence, the practice of initial cytoreductive surgery has once again been drawn into question, given that new targeted systemic therapies may control both local and distant disease.
Some have argued for a new phase III randomized trial to define the role of nephrectomy in the setting of planned targeted therapy with kinase inhibitors. In fact, French investigators have planned such a trial with sunitinib. Others have suggested, in the absence of complete responses to systemic therapy with these novel agents, surgical resection remains an important component of multidisciplinary therapy for patients with metastatic disease. What may be a more interesting and relevant question is the timing of nephrectomy relative to systemic therapy, rather than whether nephrectomy should be performed at all. “Neoadjuvant” or presurgical approaches, in which patients receive systemic therapy for a defined period before nephrectomy with resumption of therapy after recovery from surgery, are now being investigated in phase II clinical trials (65). Initial results suggest the practice is safe, but whether it represents an incremental advance over the standard practice of upfront nephrectomy remains to be determined.

The other role for surgery in the setting of metastatic RCC is the practice of metastasectomy. In the setting of an isolated metastasis, reasonably durable disease-free survival in the range of 35% at 5 years has been realized with surgical resection alone (66). Other indications for metastasis resection include symptomatic palliation of threatening disease (brain metastases, spinal cord compression, pathologic fracture), but also as a surgical consolidation strategy after response to systemic therapy (67). What remains clear is that patient selection is critical to success in these endeavors.

Summary

The incidence of RCC is increasing. More frequent use of abdominal imaging is partially responsible for this rise, through the diagnosis of asymptomatic renal masses, but there has been an increased incidence of more aggressive, advanced disease as well. Surgical therapy is a mainstay of treatment in all aspects of the disease—from localized to metastatic—with more recent efforts focused on minimizing invasiveness while maintaining oncologic equipoise with open surgical strategies. Research that has focused on the molecular changes associated with renal carcinogenesis and progression has resulted in significant improvements in patient outcome, but much more work is needed to meaningfully impact the natural history of this disease.

References

16 Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

Renal Cell Carcinoma: Overview, Diagnosis, and Surgical Treatment

Renal Cell Carcinoma: Pathologic and Molecular Characteristics

Ming Zhou, MD, PhD

Many different types of benign and malignant tumors of the kidney have been described. Accounting for more than 90% of all malignancies in adult kidneys, renal cell carcinoma (RCC) is derived from the epithelial cells of the renal tubules. It encompasses a group of heterogeneous tumors with distinct clinical, pathologic, and genetic characteristics, as well as diverse prognoses and therapeutic responses.

Pathologic Classification of Renal Cell Carcinomas

The pathologic classification of RCC serves three purposes: (a) to reflect the underlying pathogenetic mechanisms, (b) to provide clinically relevant prognostic information, and (c) to provide guidance to therapy. Table 1 lists the current classifications of RCC, published by the World Health Organization (WHO) in 2004 (1). This system is based primarily on morphology, even though morphologic classification is inherently imprecise, as different types of RCCs may exhibit similar morphology, whereas different histologic subtypes of RCC have characteristic cytogenetic and molecular changes. Some of these characteristic genetic and molecular features have already been incorporated into the WHO classification. For example, the RCC associated with Xp11.2 translocation is characterized by chromosomal translocations involving the TFE3 gene on chromosome Xp11.2. Although morphologically it overlaps with, and may be mistaken for, clear cell or papillary RCC, it is a distinct clinicopathologic entity based on this characteristic genetic change (2). In the foreseeable near future, classification of RCC based on morphology will still dominate. However, additional
molecular and genetic criteria will also be incorporated into the classification scheme. It is hoped that a classification based on morphologic, molecular, and genetic characteristics will provide not only more accurate pathologic classification, but also better prognostic and therapeutic information, and may help design more specific, genetically based therapeutic strategies.

**Pathologic and Molecular Characteristics of Subtypes of Renal Cell Carcinoma**

**Renal Cell Carcinoma, Clear Cell Type**

**Clinical Features**

RCC, clear cell type (CCRCC) is the most common histologic subtype, accounting for 60%–70% of all RCCs. It most commonly affects patients in their sixth and seventh decades of life, and men are predominantly affected, with a male to female ratio of 2:1. The majority of CCRCCs arise sporadically, with <5% of the cases presenting as part of an inherited cancer syndrome (3), including von Hippel-Lindau syndrome, Birt-Hogg-Dube (BHD) syndrome, and constitutional chromosomal 3 translocation syndrome. As a
general rule, familial CCRCC presents at a younger age and is much more likely to be multifocal and bilateral.

**Pathology**

CCRCC presents as a round, well-circumscribed, non-encapsulated mass with hemorrhage, necrosis, cystic degeneration, and calcification (4). A golden yellow color is characteristic (Figure 1A). Multicentricity and/or bilaterality occur in <5% of sporadic CCRCC cases, but they are more often associated with inherited cancer syndromes.

Microscopically, the tumor cells have clear cytoplasm (see Figure 1B) due to loss of cytoplasmic lipid and glycogen contents during the preparation of slides, hence the term “clear cell” subtype. Poorly differentiated CCRCC, however, often acquires more eosinophilic and granular cytoplasm. The term “granular cell RCC” was used in the past for RCC with eosinophilic and granular cytoplasm and high-grade nuclei. Although some RCCs with “granular” cytoplasm are now classified as CCRCC, many are of other histologic subtypes. Therefore, “granular cell RCC” is not considered a specific subtype. The term is antiquated, and its use is discouraged.

Sarcomatoid differentiation is found in approximately 5% of the cases and is indicative of poor prognosis (5). “Rhabdoid” cells with large eccentric nuclei, macronucleoli, and prominent acidophilic globular cytoplasm are occasionally seen and are also associated with poor prognosis (6).

**Molecular Genetics**

The vast majority of sporadic CCRCC harbors alterations of chromosome 3p (7,8), which houses several important genes, including the von Hippel-Lindau (VHL) gene on

![Figure 1](image-url). Renal cell carcinoma, clear cell type forms a multinodular mass with distinctive yellow and light orange color (A). It is composed of compact nests of tumor cells with clear cytoplasm separated by delicate vasculature (B).
chromosome 3p25-26, RASSF1A and DRR1 on 3p21-22, and FHIT on 3p11-12. Duplication of 5q22-pter is the second most common cytogenetic finding and may be associated with a more favorable prognosis. Other cytogenetic alterations affect 6q, 8p, 9, 11q, 14q, 17p, 18q, and 19p. Overall, 22%–71% of sporadic CCRCC cases carry mutations in the VHL gene, and another 20% harbor promoter hypermethylation, which also inactivates the VHL gene expression (9). Together, inactivation of both VHL alleles by various mechanisms occurs in >70% of sporadic CCRCC.

The VHL gene was initially identified as being responsible for von Hippel-Lindau disease (VHLD) (3). VHLD patients carry germline mutations in the VHL gene and have a propensity to develop tumors of the central nervous system, adrenal gland, pancreas, and kidney, including CCRCC. The disease is autosomal dominant with high penetrance and earlier age of onset (37 years compared to 61 for sporadic CCRCC). Affected individuals have a 70% risk of developing a renal tumor by the seventh decade.

The VHL gene functions as a tumor suppressor, with a loss of both alleles required for tumor development. VHLD patients are born with a germline defect in one of the alleles; inactivation of the second allele results from somatic mutation or hypermethylation of the gene promoter and provides the impetus for uncontrolled cell growth and tumor formation.

VHL protein plays a critical role in the cellular response to hypoxia. It forms with several other proteins a complex that targets cellular proteins for ubiquitin-mediated degradation (Figure 2) (10). One such substrate is hypoxia-inducible factor (HIF). Under normoxic conditions, HIF is hydroxylated. VHL protein binds to and targets the hydroxylated HIF for degradation. The net result is low HIF levels within normal cells. Under hypoxic conditions, when HIF is not hydroxylated, or when there is no functional VHL around due to VHL mutation or promoter hypermethylation, HIF cannot bind to VHL and is therefore not directed for degradation. Consequently, HIF accumulates within cells and activates many hypoxia-inducible genes, including genes in angiogenesis (vascular endothelial growth factor [VEGF]), cell growth (platelet-derived growth factor β, and transforming growth factor α), glucose transport (Glut-1), acid-base balance (carbonic anhydrase IX), and red cell production (erythropoietin), which then activate many intracellular signal transduction pathways, including the PI3 kinase-Akt-mammalian target of rapamycin (mTOR) and Ras-raf-erk-mek pathways. These pathways are involved in numerous cellular processes, including cell prolif-

Figure 2. Molecular pathways involving the von Hippel-Lindau (VHL) gene. Under normoxic conditions, VHL directs hypoxia-inducible factor (HIF) for proteolytic degradation. Under hypoxic conditions or when VHL is mutated or absent, HIF accumulates and activates multiple target genes, which in turn function in multiple signal transduction pathways, including PI3K-AKT-mammalian target of rapamycin (mTOR) and Ras-raf-erk-mek, to control cell proliferation, survival, growth, and differentiation. Several small molecule inhibitors can block various steps in these pathways. EPO = erythropoietin; CA IX = carbonic anhydrase IX; EGFR = epidermal growth factor receptor; PDGF-β = platelet-derived growth factor-β; TGF-α = transforming growth factor-α; VEGF = vascular endothelial growth factor.
24 Renal Cell Carcinoma: Pathologic and Molecular Characteristics

These growth factors serve a beneficial role by stimulating angiogenesis and compensatory metabolic changes in normal cells, but also contribute to the tumorigenesis and many clinical manifestations of CCRCC if the expression is uncontrolled. Many clinical trials are targeting the critical components of these pathways, including VEGF, using neutralizing antibody bevacizumab, VEGF receptor, and platelet-derived growth factor receptor using small molecule inhibitors of tyrosine kinase, such as sorafenib and sunitinib, epidermal growth factor receptor using erlotinib, and mTOR using temsirolimus, in the treatment of advanced stage CCRCC (11).

Renal Cell Carcinoma, Papillary Type

Clinical Features

RCC, papillary type (PRCC) accounts for 10%–15% of RCCs, with the gender and age distribution similar to that of CCRCC. PRCC, however, has a better prognosis than CCRCC, with a 5-year survival approaching 90%.

Pathology

PRCC forms a well-circumscribed, discrete mass with a capsule. Hemorrhage and necrosis are also common, especially in large tumors (Figure 3A). Bilateral and multifocal tumors are more common in PRCC than in other RCC subtypes. Microscopically, PRCC is comprised of variable proportions of papillae, tubulopapillae, and tubules (see Figure 3B). PRCC can further be divided into types 1 and 2 based on its morphologic features.

Figure 3. Renal cell carcinoma, papillary type has a capsule and extensive hemorrhage and necrosis (A). It is composed of papillary structures (B).
These two types of PRCC differ in genetic characteristics as well as clinical outcomes, with a better prognosis observed for type 1 PRCC.

**Molecular Genetics**

The most common cytogenetic changes observed in PRCC and its presumptive precursor lesion, papillary adenoma, are chromosomal gain, including tri- or tetrasomy 7 and 17, and loss of Y chromosome (13). Loss of heterozygosity at 9p13 is associated with shorter survival. Types 1 and 2 PRCC possess distinct genetic features, with 7p and 17p gains more commonly seen in type 1 PRCC. Patterns of allelic imbalance are also distinct between type 1 and 2 PRCC.

PRCC infrequently occurs in the setting of inherited cancer syndromes, including hereditary papillary RCC syndrome (HPRCC) and hereditary leiomyomatosis and RCC syndrome (HLRCC) (3). HPRCC is caused by mutations in \( c-met \) proto-oncogene (14) on chromosome 7q31 and develops RCC of type I histology. \( c-met \) gene encodes a protein that is the cell surface receptor for the hepatocyte growth factor (HGF) and has receptor tyrosine kinase activity. Gain-of-function mutations in \( c-met \) result in increased cellular processes that contribute to carcinogenesis, including angiogenesis, cell motility, proliferation, and morphogenic differentiation. However, \( c-met \) mutations are detected in only 13% of cases of sporadic PRCC (14). The inhibitors of the tyrosine kinase domain of MET are currently under development to treat patients with HPRCC syndrome.

HLRCC is an autosomal dominant disease and contains mutations in the fumarate hydratase (\( FH \)) gene on chromosome 17. Patients are at risk for cutaneous and uterine leiomyomas and PRCC of type 2 histology (14). \( FH \) is a key regulator of the Krebs cycle. A recent study demonstrated that inactivation of \( FH \) also correlated with HIF overexpression and potentially HIF regulated pathways (15).

**Renal Cell Carcinoma, Chromophobe Type**

**Clinical Features**

RCC, chromophobe type (ChRCC) accounts for approximately 5% of RCCs. Most cases are sporadic, although rare familial cases are associated with BHD syndrome (3). The prognosis is significantly better than CCRCC with mortality less than 10%.

**Pathology**

ChRCC is usually a solitary, circumscribed, and nonencapsulated mass with a homogeneous light brown cut surface (Figure 4A). The tumor cells are large and polygonal and have finely reticulated cytoplasm due to numerous cytoplasmic microvesicles, a prominent cell border resembling plant cells, and irregular, often wrinkled, nuclei with perinuclear clearing (Figure 4B). The cytoplasm is pale as if it is resistant to staining with
Renal Cell Carcinoma: Pathologic and Molecular Characteristics

ChRCC shows extensive chromosomal loss, most commonly involving chromosomes 1, 2, 6, 10, 13, 17, and 21 (13). Occasionally, ChRCC can occur in BHD syndrome, an autosomal dominant disorder characterized by benign skin tumors (fibrofolliculomas, trichodiscomas of hair follicles, and skin tags), renal epithelial neoplasms, and spontaneous pneumothorax. Renal neoplasms are often multifocal and bilateral and present in the forms of ChRCC, oncocytomas, hybrid oncocytoic tumors with features of both ChRCC and oncocytoma, CCRCC, and occasionally PRCC. BHD, the gene implicated in the syndrome, encodes a potential tumor suppressor protein folliculin on 17p11.2 (14). However, BHD mutations are rarely found in sporadic ChRCC or renal oncocytoma.

Other Uncommon Subtypes of Renal Cell Carcinoma

Other subtypes of RCC are rarely encountered in the kidney. Collectively, they account for <5% of RCC cases. However, they have clinical, pathologic, and genetic characteristics distinct from other more common subtypes, including CCRCC, PRCC, and ChRCC. The clinical, pathologic, and genetic features of these uncommon RCC subtypes are summarized in Table 2. Whether these subtypes respond to the treatment protocols for CCRCC is unknown because too few cases were studied.
Table 2. Clinical, pathologic, and genetic features of uncommon renal cell carcinoma subtypes

<table>
<thead>
<tr>
<th>RCC subtype</th>
<th>Clinical features</th>
<th>Pathology</th>
<th>Genetics</th>
<th>Prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilocular cystic RCC</td>
<td>Variant of CCRCC (5% of CCRCC); mean age, 51 yr (20–6); male:female = 3:1</td>
<td>Well-circumscribed, entirely cystic mass; without grossly solid area or microscopically expansile cellular nodules; low-grade nuclei (Fuhrman nuclear grade 1 or 2)</td>
<td>Same as CCRCC</td>
<td>Favorable; no local or distant metastasis after complete surgical removal</td>
<td>18</td>
</tr>
<tr>
<td>Carcinoma of the collecting ducts of Bellini</td>
<td>Aggressive tumor arising in the collecting ducts of Bellini; one-third presenting with metastasis</td>
<td>Poorly circumscribed, centrally located mass; tumor cells form complex tubulocystic structures; desmoplastic stroma</td>
<td>Limited; loss of heterozygosity on chromosomes 1q, 6p, 8p, 13q, and 21q; Her2/neu amplification</td>
<td>Poor; two-thirds of patients die of disease within 2 yr of the diagnosis</td>
<td>1</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Almost exclusively in patients with sickle cell hemoglobinopathies or sickle cell trait; mean age, 22 yr (10–40); male:female = 2:1</td>
<td>Poorly circumscribed, centrally located mass; high-grade tumor cells in solid sheets or microcystic pattern; desmoplastic stroma</td>
<td>Not well defined</td>
<td>Highly aggressive</td>
<td>1</td>
</tr>
</tbody>
</table>

(continued)
Table 2. Clinical, pathologic, and genetic features of uncommon renal cell carcinoma subtypes (Continued)

<table>
<thead>
<tr>
<th>RCC subtype</th>
<th>Clinical features</th>
<th>Pathology</th>
<th>Genetics</th>
<th>Prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xp11.2 translocation carcinoma</td>
<td>Typically affect children and young adults; accounts for one-third to 40% of RCCs in this age group; RCC involving ASPL-TFE3 translocation characteristically presents at advanced stage and also with lymph node metastasis</td>
<td>Morphology varies with different chromosomal translocations; most distinctive histologic feature: papillary structures lined with clear cells; confirmatory test: nuclear immunostain for TFE3 protein</td>
<td>Chromosomal translocation involving TFE3 gene on chromosome Xp11.2, resulting in over-expression of the TFE3 protein; translocation partner genes include PRCC on 1q21, ASPL on 17q26, PSL on 1p34, and NonO on Xq12</td>
<td>Not well defined; RCC involving ASPL-TFE3 translocation presents at advanced stage, but with indolent clinical course; adult patients may pursue aggressive course</td>
<td>2, 19</td>
</tr>
<tr>
<td>Mucinous tubular spindle cell carcinoma</td>
<td>Mean age, 53 yr (17–82); male:female = 4:1; most cases incidental finding</td>
<td>Elongated cords and collapsed tubules with slit-like spaces embedded in a lightly basophilic myxoid background; low-grade nuclei</td>
<td>Not well defined; chromosomal losses involving chromosomes 1, 4, 6, 8, 13, and 14, and gains involving 7, 11, 16, and 17</td>
<td>Favorable: majority of the patients free of disease after surgical resection</td>
<td>20, 21</td>
</tr>
<tr>
<td>Carcinoma associated with neuroblastoma</td>
<td>In long-term survivors of neuroblastoma; male:female = 1:1; age at neuroblastoma diagnosis: ≤2 yr; age at RCC diagnosis: 13.5 yr (2–35)</td>
<td>Many tumors are typical CCRCC; some tumors have solid and papillary architecture with oncocytoid cells</td>
<td>Not well defined; loss of multiple chromosomal loci observed</td>
<td>Similar to other common RCC subtypes</td>
<td>22</td>
</tr>
</tbody>
</table>

CCRCC = renal cell carcinoma, clear cell type; RCC = renal cell carcinoma.
Renal Cell Carcinoma, Unclassified Type

Two percent to 5% of RCCs do not fit into any of the subtypes in the 2004 WHO classification and are therefore called “renal cell carcinoma, unclassified type.” They represent a heterogeneous group of tumors with little in common in terms of clinical, morphologic, or genetic features. It is important to bear in mind that RCC of unclassified type is a diagnostic category, rather than a true biologic entity. As the understanding of RCC increases, this category is destined to regress and perhaps eventually to disappear.

Papillary Adenoma

**Clinical Features**
Papillary adenoma is benign and is the most common renal cell neoplasm. It is frequently an incidental finding in autopsies. In one autopsy study, papillary adenomas were found in up to 40% of patients older than 70 years of age. Its incidence increases with age and also in patients on long-term dialysis, with acquired renal cystic disease, or in scarred kidneys in patients with chronic pyelonephritis or renal vascular disease.

**Pathology**
Papillary adenomas appear as well-circumscribed, yellow, or white nodules in the renal cortex. They have a papillary, tubular, or tubulopapillary architecture, similar to PRCC, but are <5 mm, according to the WHO classification (1). The cells lining those structures have uniform small nuclei and inconspicuous nucleoli similar to Fuhrman grade 1 or 2 nuclei.

**Molecular Genetics**
The earliest genetic changes observed in papillary adenomas are combined trisomy 7 and 17, and loss of chromosome Y, changes that are also present in PRCC (13). Additional genetic alterations have been reported as they evolve. Therefore, papillary adenoma is postulated to be the precursor to PRCC.

Renal Oncocytoma

**Clinical Features**
A benign renal epithelial neoplasm, renal oncocytomas account for 5% of renal cell neoplasms. They occur in a wide age range, with a peak incidence in the seventh decade of life. Most cases are sporadic, although familial cases have been reported in association with BHD syndrome and familial renal oncocytoma syndrome (3).
30 Renal Cell Carcinoma: Pathologic and Molecular Characteristics

Pathology
Oncocytomas are typically solitary, well-circumscribed, non-encapsulated tumors (Figure 5A) with a homogeneous cut surface and a characteristic mahogany-brown color (4). A central stellate scar is seen in one-third of cases, more commonly in larger tumors. Microscopically it is characterized by bright eosinophilic cells, termed “oncocyes,” arranged in a nested, acinar, or microcystic pattern associated with a loose hypocellular and hyalinized stroma (see Figure 5B). Extension of oncocytoma into the perinephric fat or, rarely, into vascular space, can sometimes be found and does not seem to adversely affect the benign nature of the lesion.

Molecular Genetics
Most oncocytomas are composed of a mixed population of cells with normal and abnormal karyotypes (13). Some cases display loss of chromosomes 1 and 14. Occasionally, t(5; 11) is observed. Oncocytoma can be a manifestation of BHD syndrome (14). Oncocytoma and ChRCC share several cytogenetic changes, including loss of chromosome 1 (15). Whether they are genetically related and whether oncocytoma evolves into ChRCC is controversial.

Sarcomatoid Renal Cell Carcinoma
Sarcomatoid differentiation can be found in any RCC subtypes (5), and is therefore not considered as a distinct subtype of RCC by current WHO classification. Rather, it is...

Figure 5. Renal oncocytoma forms a solitary, well-circumscribed mass with homogeneous dark brown cut surface and a central scar (A). It consists of uniform tumor cells with granular eosinophilic cytoplasm and regular round nuclei nested in a loose hypocellular and hyalinized stroma (B).
thought to represent transformation to a more aggressive and higher grade RCC. The classification of such RCC should be based on the identification of the coexisting RCC components. Sarcomatoid differentiation is present in 1.0%–6.5% of RCCs. Histologically, the sarcomatoid component ranges from malignant spindle cells to those resembling leiomyosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and other sarcomas. Sarcomatoid differentiation is considered as an adverse pathologic parameter and is graded as Fuhrman nuclear grade 4 (see next section) (5). RCC with sarcomatoid differentiation often presents as high-stage and high-grade disease with frequent distant metastasis. Sarcomatoid differentiation, even when present as a small component in an RCC, significantly affects the prognosis adversely.

**Fuhrman Grading for Renal Cell Carcinoma**

The Fuhrman grading system is the most commonly used grading system for RCC. It is based on the nuclear size, irregularity of the nuclear membrane, and nucleolar prominence and categorizes RCCs into grades 1–4. Fuhrman grade can be further grouped into low grade (grade 1 and 2) and high grade (grade 3 and 4). Such grade compression not only preserves the prognostic significance of the Fuhrman grading but also improves the interobserver agreement (16).

Most studies have confirmed that Fuhrman grading is an independent prognostic predictor for CCRCC and RCC, not otherwise specified (16). However, its prognostic significance for PRCC and ChRCC remains controversial. A recent study suggested Fuhrman grading is not prognostically useful for ChRCC (17).

**Optimal Handling of Renal Cell Carcinoma Specimens**

The optimal handling of RCC specimens by pathologists is critical because the pathologic examination not only provides a diagnosis, but also delivers information important for a prognosis and subsequent therapeutic decisions. In addition, redundant tumor tissues not required for diagnosis could be procured for clinical trials, experimental therapies, and research. It is important to realize that urologists and medical oncologists also play an important role in this process. Urologists should try to preserve the anatomy of the nephrectomy specimen. If the perinephric fat has to be separated from the kidney for any reason, it should be oriented and the zone of tumor contact should be indicated. Lymphadenectomy specimens should be submitted in a separate container. If the lymphadenectomy is not separated from the perihilar tissue, pathologists should be made aware of this information so that they can look for the lymph nodes in the nephrectomy specimens. The specimen should be sent to pathology fresh without fixative in a sterile fashion immediately after its removal from the patient. Fix the specimen in formalin only if the delivery of the specimen is expected to be delayed or no molecular or cytogenetic
studies are anticipated. The importance of the availability of fresh tumor tissue for molecular and cytogenetic studies could not be overemphasized. Approximately 2%–5% of renal tumors remain unclassified using the current WHO classification. Molecular and genetic approaches offer the only hope that these “unclassifiable” RCCs would be classified based on the genetic and molecular features. Clinical information is also critical and should accompany the surgical specimens. Previous medical history, including prior renal tumors and family history, is extremely important for identifying familial RCC cases. Awareness of such history prompts pathologists to preserve fresh tumor tissues for molecular and genetic study and order additional tests to work up the case.

Summary

RCC represents a group of heterogeneous tumors with distinct clinical, pathologic, and genetic characteristics and diverse prognoses and therapeutic responses. The 2004 WHO classification is the most updated classification system based on morphology and genetics. Pathologic examination of the RCC specimens not only renders diagnosis, but also provides information important for prognosis and therapeutic decisions. In addition, tumor tissues can be used for experimental studies and research. Pathologists, urologists, and medical oncologists play an equally important role in the optimal handling and processing of RCC specimens.

References

In 2007, an estimated 51,190 cases of renal cell carcinoma (RCC) will be diagnosed, accounting for roughly 3% of all malignancies in adults (1). Prognosis varies with numerous characteristics of the disease, including tumor anatomy and histology. Paralleling the trend in the development of molecular therapeutics for RCC is the development of various genetic and biochemical profiling techniques to refine prognosis. In addition to providing physicians and patients with valuable insights into the nature of the disease, these techniques may also help reveal previously unrecognized therapeutic targets and allow patient selection for treatment. In this chapter, we review the evolution of traditional staging systems for RCC and the incorporation of clinical and molecular profiling to enhance the accuracy of prognosis.

Evolution of the Tumor, Node, and Metastasis Staging System

Tumor Size

The tumor, node, metastasis (TNM) staging system (Table 1) was revised in 1997 to increase the tumor cutoff size for T1 disease from 2.5 to 7.0 cm, reflecting improving trends in survival of patients with larger tumors (Table 2) (2). Prognosis varies with tumor size, with 5-year survival rates of 84%, 50%, and 0% for tumors measuring less than 5 cm, 5–10 cm, and greater than 10 cm, respectively (3). Several studies report disagreement about the optimal tumor cutoff size for prognosis, with values of 4.5, 5.0,
5.8, 8.0, and 10.0 cm suggested (4). Classification of tumors within the T1 category developed further significance with the establishment of the safety and efficacy of nephron-sparing surgery. Hafez et al. suggested that nephron-sparing surgery, when used for tumors larger than 4 cm, led to an increased risk of recurrence and poorer survival rates (5). In 2002, the T1 category was segregated into two groups, T1a and T1b, representing tumors smaller and larger than 4 cm, respectively (4). This T1a cutoff was disputed more recently by Ficarra et al., who suggested that patients with tumors smaller than 5.5 cm

Table 1. American Joint Committee on Cancer staging system for renal cell carcinoma

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX  Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0  No evidence of primary tumor</td>
</tr>
<tr>
<td>T1  Tumor 7 cm or less in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1a Tumor 4 cm or less in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T1b Tumor more than 4 cm, but not more than 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T2  Tumor more than 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td>T3  Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3a Tumor directly invades the adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota’s fascia</td>
</tr>
<tr>
<td>T3b Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches or vena cava below the diaphragm</td>
</tr>
<tr>
<td>T3c Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava</td>
</tr>
<tr>
<td>T4  Tumor invades beyond Gerota’s fascia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX  Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0  No regional lymph node metastases</td>
</tr>
<tr>
<td>N1  Metastases in a single regional lymph node</td>
</tr>
<tr>
<td>N2  Metastases in more than one regional lymph node</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX  Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0  No distant metastases</td>
</tr>
<tr>
<td>M1  Distant metastases</td>
</tr>
</tbody>
</table>

may be amenable to nephron-sparing surgery; however, the TNM staging system remains unchanged at this time (see Table 1) (6).

The increased threshold for T1 disease in 1997 led to a change in criteria for inclusion in T2 disease, which now includes tumors larger than 7 cm in size and limited to the

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Prognostic value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>Key component of the tumor, node, metastasis (TNM) staging system and remains one of the most important prognostic factors within T stage</td>
</tr>
<tr>
<td>Perinephric/renal sinus fat involve-ment</td>
<td>Portends a worse prognosis, but renal sinus fat involvement is associated with a higher risk of death compared to peripheral perinephric fat involvement</td>
</tr>
<tr>
<td>Adrenal gland involvement</td>
<td>Currently classified as stage T3a, but direct adrenal gland invasion is associated with worse outcomes compared to perirenal fat involvement</td>
</tr>
<tr>
<td>Venous tumor thrombus extension</td>
<td>High risk for recurrent disease</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>Portends a poor prognosis</td>
</tr>
<tr>
<td>Presence of distant metastases</td>
<td>Portends a poor prognosis</td>
</tr>
<tr>
<td></td>
<td>Unresected positive lymph nodes respond poorly to immunotherapy</td>
</tr>
<tr>
<td></td>
<td>N1–N2 subclassification remains controversial</td>
</tr>
<tr>
<td></td>
<td>Extramedullary extension portends a poorer prognosis</td>
</tr>
<tr>
<td></td>
<td>Practice and extent of lymphadenectomy remains unstandardized</td>
</tr>
<tr>
<td></td>
<td>Number of metastatic sites, rather than actual location, dictates overall prognosis</td>
</tr>
<tr>
<td></td>
<td>Cytoreductive nephrectomy with postoperative immunotherapy improves survival in select patients</td>
</tr>
<tr>
<td></td>
<td>Solitary metastasis is a favorable prognostic factor over multiple metastases</td>
</tr>
<tr>
<td></td>
<td>Metachronous metastases are a favorable factor over synchronous metastases</td>
</tr>
</tbody>
</table>

IVC = inferior vena cava.
kidney. However, even within the T2 group, significant variation has been observed (4). A series by Frank et al. demonstrated that tumors larger than 10 cm were more aggressive than those in the range of 7–10 cm (7). Similarly, an international multicenter trial including 639 patients with stage T2 RCC identified significant differences between groups using an upper threshold of 13 cm (8). Further stratification of T2 RCC into T2a and T2b subgroups may allow for more precise estimation of survival.

**Tumor Extension: Adrenal Invasion, Fatty Tissue Invasion, and Venous Involvement**

According to the current classification scheme, T3 disease encompasses tumors that invade major veins, the adrenal gland, or perinephric tissues enclosed within Gerota’s fascia. This category of disease contains a broad range of prognoses, with 5-year survival estimates between 37% and 67% (9). T3a tumors, which include tumors with adrenal involvement or those confined to the perirenal fat within Gerota’s fascia, have been shown to have 5-year cancer-specific mortality within a range of 36%–53% (10,11). Several studies have addressed the impact of adrenal involvement: Han et al. assessed a series of patients with T3a disease and demonstrated that those patients with adrenal involvement had significantly poorer 5-year survival (0%) when compared with those patients with perinephric fat involvement only (36%). Survival rates associated with adrenal involvement approached that for T4 disease (10).

Although adrenal involvement certainly appears to influence patient prognosis in T3a disease, the anatomic pattern of fatty involvement may lead to variations in survival. The T3a designation applies to both renal sinus and perinephric fat invasion. A retrospective study suggested that patients with renal sinus fat invasion were 63% more likely to die of RCC when compared to patients with perinephric fat invasion, and this difference persisted even after adjustment in multivariate analysis for regional lymph nodes and distant metastases (12).

Venous involvement in newly diagnosed patients with RCC occurs in 4%–9% of cases. The current TNM system distinguishes between tumors that extend into the renal vein or the vena cava below the diaphragm (categorized together as T3b disease), and tumors invading the wall of the vena cava or the vena cava above the diaphragm (T3c). Varying assessments of survival have been published within the setting of T3b disease. A study by Kim et al. compared survival in 226 patients with T3b and T3c RCC to a group of 654 patients without venous involvement. As anticipated, there was a significant increased risk of recurrence with venous involvement, and there was poorer survival in the T3c group relative to the T3b group. No differences with respect to survival were seen in patients with metastatic disease, regardless of the extent of venous involvement. Within T3b patients, there appeared to be similar survival in patients with renal vein and vena cava involvement (13). This was not the case, however, in a separate retrospective study of 153 patients with T3b and T3c disease, which showed that although survival
was similar with all levels of vena cava involvement, there was a significantly different 10-year survival rate in patients with renal vein involvement versus those patients with vena caval involvement below the level of the diaphragm (66% and 29%, respectively). These results led to the suggestion that the combination of these two groups in the T3b category should be re-evaluated (14).

**Lymph Node Involvement**

Nodal involvement is currently divided into three subgroups: (a) no regional lymph node metastases (N0), (b) a single positive regional lymph node (N1), or (c) more than one regional lymph node (N2). The incidence of lymph node involvement varies with the extent of disease; lymph node involvement in localized disease is estimated between 2% and 9%, and the occurrence in metastatic disease is estimated to be as high as 50% (15). The reported 5-year cancer-specific survival with lymph node involvement varies between 11% and 35%, suggesting a dramatic impact (15–17). Lymphadenectomy can potentially result in cure in patients with extrarenal disease limited to the lymph nodes, but prediction of involved lymph nodes is limited by available radiographic techniques. In a study by Studer et al., preoperative computed tomographs were reviewed in 163 patients to assess the predictive value for diagnosis of regional lymph node metastases. Though its sensitivity was high (95%) for predicting enlarged lymph nodes, only 42% of those identified ultimately yielded histology consistent with metastatic RCC (18).

Efforts to establish the benefit of lymphadenectomy include a study by the European Organisation for Research and Treatment of Cancer (EORTC 30881), the only prospective, randomized trial to date. The study enrolled 772 patients with clinically localized disease to receive nephrectomy with or without standardized lymphadenectomy. An interim analysis suggests no differences in time to progression or survival at 5-year median follow-up, but given the relatively high survival (82%) at this interval, more time is needed for these results to mature (13).

Several trials suggest that lymphadenopathy can have an impact on survival, even in the setting of metastatic disease. In a study by Vaselli et al., a total of 154 patients with metastatic RCC underwent cytoreductive nephrectomy as preparation for interleukin (IL)-2–based therapy. Patients with no preoperative lymphadenopathy lived longer than patients with lymphadenopathy (14.7 months vs. 8.5 months, respectively). It was also noted that incompletely resected lymphadenopathy portended a poorer prognosis (16). A separate study by Pantuck et al. sought to characterize responses to immunotherapy based on the presence or absence of lymphadenopathy. In this retrospective cohort analysis, 322 patients with metastatic RCC were included, with 236 patients with node-negative disease and 86 patients with node-positive disease. Node-negative patients were more likely to achieve an objective response to immunotherapy. Immunotherapy was shown to improve median survival in node-negative patients from 20.4 months to 28.0 months; however, no similar improvement was observed in this parameter in the node-positive population (17).
Metastatic Disease

An estimated 20%–30% of patients with RCC present with metastatic disease, and metastatic disease will ultimately develop in 20%–40% of patients undergoing nephrectomy for localized disease (19). The general prognosis for metastatic disease is poor, with a median survival ranging from 6 to 10 months; however, features such as the location of the metastases may affect prognosis within this class of disease (20). Seaman et al. performed a retrospective review of 90 patients with metastatic disease at various sites. Analysis showed that bone metastases were associated with a significantly worsened median survival as compared to metastatic disease at other sites (13.8 vs. 25.3 months) (21). A separate study by Han et al. suggested the number of metastatic sites was useful in determining outcomes in metastatic disease. The retrospective analysis of 434 patients included 120 patients with metastases to the lung only, 33 patients with metastases to the bone only, and 144 patients with multiple organ involvement. Median survival was significantly reduced in patients with multiple sites of metastases (13 months) as compared to metastases to the bone or lung alone (31 months in both groups). There was also a decrease in the response to immunotherapy in the former group (22).

Histologic Features and Prognosis

Tumor Grade

The most frequently used grading system for RCC, the Fuhrman grading system, was devised in 1982 and is comprised of four nuclear grades (1–4) defined by increasing nuclear size, irregularity, and nucleolar prominence (23). The association of Fuhrman grade and prognosis has been established in several studies (Table 3). Bretheau et al. performed a retrospective analysis of 190 patients with RCC treated with radical nephrectomy and noted that there was a significant correlation between nuclear grade and tumor stage, synchronous metastases, lymph node involvement, renal vein involvement, tumor size, and perirenal fat involvement. A downward trend was also observed with increased grade, with 5-year actuarial survival rates of 76% in grade 1, 72% in grade 2, 51% in grade 3, and 35% in grade 4 disease. The combination of grades 1 and 2 showed significantly improved survival in comparison to grades 3 and 4 (24). Further evidence of the utility of the Fuhrman grading system comes from a larger retrospective study by Tsui et al. (9) in which 643 patients were evaluated on the basis of nuclear grade and several other variables, including TNM stage and Eastern Cooperative Oncology Group (ECOG) performance status. Survival rates based on grade were 89% for grade 1, 65% for grade 2, and 46% for grades 3 and 4 combined, with nuclear grade and TNM stage exhibiting the highest correlation with survival among other factors (9).
Prognostic Factors in Renal Cell Carcinoma Patients

Table 3. Summary of histologic and clinical features related to prognosis in renal cell carcinoma (RCC)

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Prognostic value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear grade</td>
<td>Four-tier system based on nuclear size, nuclear contour, and presence of prominent nucleoli Higher grade portends poorer prognosis</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Chromophobe subtype historically associated with favorable prognosis, but emerging data suggest no difference between histologic subtypes after stratifying for stage and grade Type 2 papillary RCC associated with poorer prognosis compared with type 1 papillary RCC Non-clear cell RCC responds poorly to systemic immunotherapy</td>
</tr>
<tr>
<td>Sarcomatoid features</td>
<td>High-grade form typified by a spindle cell growth pattern Associated with poor prognosis</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>Presence and extent of histologic tumor necrosis portends poorer prognosis</td>
</tr>
<tr>
<td>Collecting system invasion</td>
<td>Associated with poorer prognosis in low-stage tumors (T1–T2)</td>
</tr>
<tr>
<td>Microvascular invasion</td>
<td>Associated with higher disease progression, recurrence, and death</td>
</tr>
<tr>
<td>Performance status</td>
<td>Poorer performance status associated with worse prognosis</td>
</tr>
<tr>
<td>Paraneoplastic symptoms</td>
<td>Cachexia-related findings include hypoalbuminemia, weight loss, anorexia, and malaise Presence of cachexia-related findings portends poorer prognosis</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>Independent predictor of poor prognosis</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Elevated serum C-reactive protein and erythrocyte sedimentation rate associated with poorer prognosis</td>
</tr>
</tbody>
</table>


Histologic Type

The four primary histologic types of RCC are clear cell (CCRCC), papillary (PRCC), chromophobe (ChRCC), and collecting duct, as established by the International Union against Cancer and the American Joint Committee on Cancer (25). CCRCC is the most common, representing 70%–80% of all RCC, followed by PRCC, representing roughly 20%. ChRCC accounts for only 5% of RCC, and collecting duct carcinoma is a rare variant (26). The correlation between prognosis and histologic type is less clear than that with nuclear grade. A study by Amin et al. assessed 377 patients with RCC further characterized by sub-
42 Prognostic Factors in Renal Cell Carcinoma Patients

type. After a mean follow-up of 64.5 months in 368 patients, disease-specific survival and progression-free survival were noted to be correlated with histologic type, as well as TNM stage, Fuhrman grade, vascular invasion, and necrosis. However, in a multivariate analysis, histologic type was not determined to be an independent predictor of survival (27).

A study of 2,385 patients treated at the Mayo Clinic with radical nephrectomy for sporadic, unilateral RCC was subsequently reported, with 5-year, cancer-specific survival rates of 68.9%, 87.4%, and 86.7% for CCRCC, PRCC, and ChRCC, respectively. The survival in the clear cell group was noted to be significantly lower than that of the other two groups, even after controlling for TNM stage and nuclear grade. No differences were detected in survival between the papillary and chromophobe subtypes (28). A larger international multicenter study of 4,063 patients with RCC assessed prognosis across the same three subtypes. Median survival times were 119 months, 153 months, and not reached in clear cell, papillary, and chromophobe subtypes, respectively, with a significant trend toward improved survival in these groups. However, once again, histologic type did not retain independent prognostic significance in multivariate analysis (29).

It is unclear whether further distinction of histologic subtypes will lead to better predictive capabilities in survival outcomes. For instance, novel molecular techniques have allowed for the identification of two separate types of PRCC. Analysis of gene expression profiles of 34 cases of RCC using Affymetrix gene arrays yielded two distinct genetic signatures (types I and II), and these were validated by immunohistochemical techniques in 15 tumors. As a result, it was noted that the less aggressive type I PRCC had high expression of cytokeratin 7, whereas the more aggressive type II PRCC had high expression of topoisomerase-α-2 (30).

Though these novel characterizations of histologic subtypes may ultimately demonstrate prognostic utility, there is limited evidence of this at the present time. Predicting therapeutic response in relation to histologic subtype, however, does appear to have rationale. Upton et al. assessed 163 patients with primary RCC who received IL-2 therapy for their disease and noted a 21% response rate for patients with CCRCC, versus 6% in patients with variant or indeterminate-type RCC (31). A similar result was noted in a report by Motzer et al. of 64 patients with non-clear cell RCC. It was noted that the response to systemic therapy and survival was poor in these groups, with chromophobe tumors exhibiting the best prognosis and response among the non-clear cell subtypes (32).

Tumor Necrosis

Several studies have associated necrosis in tumor specimens with worsened prognosis. Lam et al. reviewed the clinical features of 311 patients with RCC on the basis of necrosis as well as TNM stage, nuclear grade, ECOG performance status, disease recurrence, and survival. The presence of necrosis was associated with a higher T classification by TNM staging, positive lymphadenopathy, presence of metastases, and higher grade. Necrosis in the primary tumor was associated with a lower 5-year, disease-specific survival (36%) compared to survival in patients without necrosis in the primary tumor (75%). Multivariate analysis, however, suggested that, whereas T classification, distant metastases, and ECOG performance
status were independent predictors of disease-specific survival, the presence of necrosis was not. But when patients were further stratified into groups based on localized and metastatic disease, necrosis was identified as an independent predictor of survival (33).

Tumor necrosis was assessed in a larger retrospective series from the Mayo Clinic derived from a registry of 3,009 patients who received nephrectomy for RCC. Tumor necrosis was present in 28% of clear cell, 47% of papillary, and 20% of chromophobe subtypes. Corresponding risk ratios for death were 5.27, 4.20, and 1.49, respectively. It was noted that CCRCC was associated with a worse prognosis, even after multivariate adjustment for tumor stage, tumor size, and nuclear grade. On the basis of these findings, the authors suggested the use of tumor necrosis as a prognostic indicator specifically in the settings of CCRCC and ChRCC (34).

Collecting System Invasion

Several retrospective studies have evaluated the impact of collecting system invasion on RCC. Uzzo et al. reviewed nephrectomy specimens from 426 RCC patients, finding collecting system invasion in 61 (14%) of cases, the majority representing clear cell and sarcomatoid histology. Higher nuclear grade was associated with collecting duct invasion, with 70% of the specimens characterized as Fuhrman grade 3 or 4. Prognosis in this group was generally poor, with a median disease-specific survival of 19 months (35). In a larger study, Palapattu et al. reviewed nephrectomy specimens from 895 patients with RCC, demonstrating a similar proportion of patients with collecting duct invasion (124 patients, or 14%) as in the prior study. This study revealed a greater likelihood for metastatic disease and positive lymph nodes in this group, and decreased 3-year overall survival was noted across all stages in the setting of invasion. The overall risk of death was 1.4 times greater in this group (36).

Collecting duct invasion was most recently assessed in the setting of more limited stage disease by Klatte et al. In this retrospective analysis of 519 patients treated with nephrectomy for stage I and II disease, it was noted that collecting system involvement occurred in roughly 7.5% of patients. Collecting system invasion was noted to be an independent prognostic factor of recurrence-free survival (with a relative risk of recurrence of 3.78) (37).

Sarcomatoid Features

Sarcomatoid RCC, initially considered to be a distinct category of RCC, is now classified based on the presence of histologic features (namely, pleomorphic spindle cells) that can occur in any subtype. Occurring in roughly 5% of all patients with RCC, sarcomatoid features generally correlate with an aggressive course (38). A study by de Peralta-Venturina et al. identified a larger series of 101 cases of sarcomatoid RCC occurring in 952 consecutively histologically subtyped cases of RCC. Decreased survival was reported to be associated with a larger percentage of sarcomatoid features. The 5- and 10-year disease-specific survival in patients with
sarcomatoid features was 22% and 13%, respectively, as compared to 79% and 76% in a cohort of patients lacking these features. The poorer prognosis with sarcomatoid features persisted after adjustment for stage, tumor necrosis, and tumor size (39).

As with other histologic characteristics of RCC, the presence of sarcomatoid features may be of use in selecting patients who may respond to particular therapeutic modalities. Cangiano et al. reviewed 31 consecutive cases of sarcomatoid RCC and assessed both clinicopathologic variables and treatment regimens. This group received a wide spectrum of treatment, including low- and high-dose IL-2, dendritic cell vaccine–based therapy, and interferon (IFN)-α–based therapy. Overall survival at 1 and 2 years was 48% and 37%, respectively. Although no correlation with prognosis was found with respect to the extent of sarcomatoid features, there was pronounced improvement in survival in patients with sarcomatoid features who received high-dose IL-2–based regimens (the risk of death was 10.4 times greater with non–high-dose IL-2–based regimens) (38).

Microvascular Invasion

Microscopic examination of RCC specimens leads to the observation of tumor invasion into blood vessels adjacent to the renal parenchyma in roughly 25% of cases. Two studies have identified the prognostic significance of microvascular invasion (40,41). Van Poppel et al. examined tumor specimens from 180 patients who underwent partial or radical nephrectomy for localized RCC with subsequent correlation to clinicopathologic variables. Multivariate analysis suggested that microvascular invasion was the single most important variable for predicting progression, with the rate of progression at 1 year estimated at roughly 45% (41). A more recent analysis of 95 patients undergoing radical nephrectomy or nephron-sparing surgery for clinically localized RCC also suggested the importance of microvascular invasion (42). Invasion was correlated with tumor size, invasion of perirenal fat, extension into the renal vein, nuclear grade, lymph node metastases, and sarcomatoid features. Of 24 patients with microvascular invasion, 12 (50%) demonstrated a recurrence, as compared to recurrence in only 4 patients (6%) among 71 patients without this feature (42).

Clinical Characteristics Affecting Prognosis

Performance Status

The ECOG performance status (ECOG-PS) is based on the ambulatory capabilities of the patient and is graded from 0 to 4 in order of decreasing function. The ECOG-PS has been shown to be a powerful predictive tool in determining prognosis in a variety of malignancies, and, in the setting of metastatic RCC, the role of the ECOG-PS scale is equally well defined (42). In their review of 643 patients with various stages of RCC undergoing partial or radical nephrectomy, Tsui et al. identified the ECOG-PS as an
independent predictor of survival, with a reported 5-year cancer-specific survival of 81% and 51% in groups with an ECOG-PS of 0 and >1, respectively (9).

Cachexia-Related Findings

Cachexia is a common finding in advanced RCC, but may also represent a paraneoplastic process. In a study by Kim et al. (43), 250 patients who had received surgery for T1N0M0 RCC were selected from an institutional database. Cachexia-related findings were classified as the complex of malaise, weight loss, anorexia, and hypoalbuminemia, and these variables were assessed in the study population. It was determined that patients with one or more symptoms of cachexia had worse recurrence-free survival and disease-specific survival rates relative to patients with no symptoms even after adjusting for tumor size, tumor grade, and performance status (43). Expanding from this experience in limited-stage disease, a separate study assessed the clinicopathologic features of 1,046 patients undergoing nephrectomy for all stages of RCC. In a multivariate analysis, it was demonstrated that cachexia-related symptoms predicted shorter survival. Of note, malaise seemed to exhibit a correlation with a decreased response to immunotherapy among the symptoms in the complex (44).

Thrombocytosis

Thrombocytosis has been linked to decreased survival in the setting of metastatic RCC. Symbas et al. (45) examined records of 259 patients with metastatic RCC who had received a variety of adjuvant therapies subsequent to nephrectomy. The patients were divided into two groups based on platelet count, with a threshold of 400,000/mm$^3$ defining thrombocytosis. Mean overall survival in patients with and without thrombocytosis was 92 and 151 months, respectively, representing a 64% increase in life expectancy (44). Gogus et al. (46) examined the same phenomenon in the setting of localized RCC. In this study, 151 patients who had undergone radical nephrectomy for localized RCC were stratified based on preoperative platelet count, using the same threshold of 400,000/mm$^3$ to define thrombocytosis. In this study, patients with thrombocytosis had a mean survival of 42 months as compared to 76.6 months in patients without (45).

Molecular Features of Renal Cell Carcinoma and Prognosis

Hypoxia-Inducible Factor

The heterodimeric hypoxia-inducible transcription factor 1 (HIF-1) is comprised of the subunits HIF-1β and aryl hydrocarbon receptor nuclear translocator. HIF-1, under con-
Prognostic Factors in Renal Cell Carcinoma Patients

HIF-1α itself has been studied as a prognostic factor in RCC. Lidgren et al. (51) assessed HIF-1α expression using immunohistochemical staining in 216 patients with varying histologic types of RCC. It was found that there was a statistically nonsignificant trend toward prolonged survival in patients with increased HIF-1α staining in CCRCC. Also in the setting of CCRCC, significant differences were noted in survival based on HIF-1α expression when compared with TNM stage, Fuhrman grade, and renal vein invasion, and tumor size was noted to correlate inversely with HIF-1α expression. Differences in survival based on HIF-1α were not observed in papillary subtypes, and analysis of ChRCC was limited by the small sample size in this study (51).

The molecular association of HIF-1α with VHL protein also suggests the role of the latter as a prognostic factor. This was explored by Yao et al. (52), in which 187 patients with CCRCC were assessed for VHL alterations (mutation or hypermethylation). Approximately 57% of these patients possessed such mutations, and it was found that VHL alterations were strongly associated with an improved cancer-specific survival in stage I–III disease. The statistical significance of these associations improved with increasing stage of disease, and VHL alterations were identified as an independent prognostic factor. In the same study, however, assessment of VHL alterations did not reveal any prognostic significance in stage IV disease (52).

Carbonic Anhydrase IX

Carbonic anhydrase IX (CA IX) is a transmembrane enzyme that may play a role in cellular adaptation to hypoxia. Normal expression is generally limited to the gastrointestinal tract, gallbladder, and pancreatic ducts, but there is dramatic overexpression in a variety of tumors, including RCC. The mechanism by which this is proposed to occur in RCC is HIF-1α accumulation as a result of tumor hypoxia, leading to subsequent up-regulation of CA IX expression. Bui et al. (53) confirmed the clinical applicability of immunohistochemical analysis of CA IX to determine prognosis. Paraffin embedded the specimens from 321 patients treated with nephrectomy for CCRCC, with staining for CA IX present in 94% of the specimens. Low CA IX was found to be an independent
predictor of poor prognosis in patients with metastatic RCC and was also associated with poorer outcomes in patients with nonmetastatic disease at a high risk for progression (i.e., by nuclear grade or nodal involvement) (53). CA IX expression is attributed to mutations in the VHL gene. In a separate analysis of 100 patients receiving radical nephrectomy, low CA IX expression was correlated with an absence of mutation as well as other aggressive tumor features (54).

CA IX may also have significant predictive value with respect to response to immunotherapy. In a study of 66 tumor specimens from patients who had undergone IL-2 therapy for RCC, 41 (62%) were found to have high CA IX expression. Median survival was prolonged in this subset of patients, and survival beyond 5 years was observed exclusively in this group (55).

Vascular Endothelial Growth Factor

The role of VEGF in the promotion of tumor growth and proliferation is a result of its function in angiogenesis, a well-established phenomenon. The accumulation of HIF-1α in RCC is a result of tumor hypoxia leading to increased transcription of VEGF via activation of HREs. The prognostic significance of VEGF in RCC was suggested by Djordjevic et al. (56), in which 93 cases of CCRCC were assessed for VEGF expression via immunohistochemistry. A positive staining for VEGF was considered one with greater than 75% of cells, and, using this threshold, an association was found between increased VEGF expression and a higher nuclear grade and Ki-67 proliferation index (56).

Although no correlation was made to clinical outcome, a separate study by Ljungberg et al. (57) addressed the issue of VEGF and patient survival. In this study, specimens from 110 patients were assessed for both expression of VEGF and related receptors: VEGF receptor 1 (VEGFR-1) and VEGF receptor 2 (VEGFR-2). The results revealed inconsistent associations between VEGF and prognosis across histologic subtypes. In the setting of CCRCC, it was noted that patients with VEGF levels below the median had a significantly shorter survival time when compared to those with VEGF levels above the median. VEGFR-2 was discovered to have a similar association with survival, with levels of VEGFR-2 higher in stage I-II disease as compared to higher stages. In contrast, in the setting of PRCC, higher levels of VEGF, VEGFR-1, and VEGFR-2 were associated with shorter survival. VEGF and its receptors were not found to be independent prognostic factors for any subtype of RCC (57).

Of note, current clinical trials of angiogenesis inhibitors (including bevacizumab) generally include only patients with CCRCC. Given the evidence of increased VEGF and VEGFR expression in PRCC correlating with poorer survival, there may be a theoretical rationale for trials of angiogenesis inhibitors in patients of this subtype. Further support for this comes from Leppert et al. (58) in which tissue microarray constructs were derived from 340 patients with CCRCC and 42 patients with PRCC. Immunohistochemical staining for VEGF ligands and receptors involved in angiogenesis pathways (i.e., VEGF-A, VEGF-2) was more prominent in the papillary subtype (58).
Prognostic Factors in Renal Cell Carcinoma Patients

Upstream Mediators of Hypoxia-Inducible Trascription Factor 1α

Genetic alterations in RCC lead to mutated VHL protein with a lower affinity for HIF-1α. Although there is extensive evidence for HIF-1α accumulation through this mechanism, there may also be contribution from upstream mediators of HIF-1α transcription and activation. Specifically, these upstream mediators include the PI3K-Akt-mammalian target of rapamycin (mTOR) pathway, linked to a number of receptor tyrosine kinases (including the epidermal growth factor family of receptors) (47). Loss of inhibitory mechanisms in this cascade can thus lead to enhanced activation of HIF-1α. One mediator of PI3K-Akt pathway inhibition is phosphatase and tensin homolog (PTEN), the loss of which is associated with aggressive disease in a variety of malignancies. In the setting of RCC, PTEN was established as a variable in an integrated clinical and molecular prognostic model. A recent study by Panton et al. (59) used a tissue microarray construct derived from 375 patients treated by nephrectomy for RCC. Based on a defined immunohistochemical staining percentage, PTEN was characterized as an independent prognostic factor (59).

Cyclin-Dependent Kinase Inhibitors

Cyclin-dependent kinase inhibitors (CKIs) participate in cell cycle regulation at various phases. The CKI 1A (p21) specifically inhibits the activity of cyclin-dependent kinases (CDKs) 2 and 4, leading to inhibition of progression beyond the G1 phase. CKI 1B (p27) similarly acts on the G1/S transition (60). Both moieties have shown correlation with prognosis in the setting of RCC. Weiss et al. (61) performed immunohistochemical analysis of 311 patients with CCRCC showing correlation of p21 staining and disease-specific survival when stratified by localized and metastatic disease. The cellular localization of p21 had some association with prognosis, which also varied in localized and metastatic disease. In the setting of localized disease, nuclear p21 was associated with a good prognosis, whereas both nuclear and cytosolic p21 staining were associated with a poorer prognosis in the setting of metastatic disease (61).

Similar to p21, expression of p27 was found to have some correlation with prognosis. A study by Hedburg et al. (62) assessed expression of CKIs in 218 RCC specimens from nephrectomized patients and found that low p27 cellular content correlated with high nuclear grade, large tumor size, and poor prognosis (62). A study by Anastasiadis et al. (63) assessed p27 expression via immunohistochemistry in 154 RCC specimens and similarly found that low expression of p27 was correlated with increased tumor grade, with lower p27 in poorly differentiated tumors relative to moderately and well-differentiated tumors (63).

Cytokines

The success of immunotherapies such as IL-2 and IFN-α in RCC suggests that genetic alterations affecting susceptibility to these agents could have a significant impact on prog-
nosis. In fact, preclinical studies have established the role of a wide variety of cytokines in RCC growth and growth inhibition. Among these cytokines is IL-4, which has a growth-inhibitory effect on RCC via specific binding to the IL-4 cell surface receptor in cellular models (64). In spite of these preclinical observations, systemic treatment with IL-4 lacks any clinical benefit. Kleinrath et al. (65) sought to determine a correlation between mutations in cytokine-encoding genes and prognosis by analyzing 21 single nucleotide polymorphisms in 13 cytokine genes. Using DNA from 80 patients with metastatic RCC, it was determined that a heterozygote with IL-4 promoter types IL4/-589T-33T and IL4/-589C-33C led to a 3.5-fold decrease in median overall survival when compared to a homozygote for IL4/-589C-33C. In addition to providing a useful molecular prognostic tool, these data may prompt a second look at IL-4 therapy in patients with these promoter variants (65).

Combining the Data: Integrated Prediction Models for Renal Cell Carcinoma

Early Prediction Models

As is the case for most malignancies, prediction models greatly assist in the decision to proceed with therapy. The first suggestion of prognostic factor utilization for further therapeutic management was published 1986. In this study by Maldazys et al. (66), clinicopathologic data were analyzed from 181 patients with various stages of metastatic RCC. Specifically, factors including age, sex, disease-free interval, performance status, sites of metastasis, and nephrectomy were assessed. It was found that improved survival correlated with longer disease-free intervals between nephrectomy and time of metastasis, normal performance status, metastasis limited to the lung, and removal of the primary tumor. The authors of the study suggested that patients with these favorable characteristics should be considered candidates for more aggressive therapy (66). A similar set of variables was used to stratify patients into prognostic groups in a study by Elson et al. (67). In their assessment of 610 patients with metastatic RCC, multivariate analysis identified ECOG-PS, the number of metastatic sites, recent weight loss, and prior cytotoxic chemotherapy as indicators of survival. From these data, a five-point scale was constructed (with each of the aforementioned variables representing one point), and survival within the five respective risk groups was 12.8, 7.7, 5.3, 3.4, and 2.1 months (68).

The Memorial Sloan-Kettering Cancer Center Experience

Motzer et al. (68) performed a retrospective analysis of 670 patients treated in 24 clinical trials at Memorial Sloan-Kettering Cancer Center (MSKCC), 394 of whom had received immunotherapy. Multivariate analysis yielded five prognostic variables associ-
Prognostic Factors in Renal Cell Carcinoma Patients

ated with decreased survival, including (a) low Karnofsky performance status (<80%), (b) high serum lactate dehydrogenase (>1.5 times upper limit of normal), (c) low hemoglobin (< lower limit of normal), (d) high serum calcium (>10 mg/dL corrected), and (e) the absence of prior nephrectomy. Based on the number of these risk factors present, patients were further stratified into three groups with an assigned prognosis (Figure 1). Patients with no risk factors were considered low risk and had a median survival of roughly 20 months. One to two risk factors (intermediate risk) was associated with a median survival of 10 months, whereas three or more risk factors (high risk) was associated with a median survival of 4 months (68).

Narrowing the focus to specific therapy rendered, a similar prognostic scale was established by the same group using data from six prospective trials of first-line IFN-α therapy (69). The same prognostic variables were used as in the previous risk model,
with the notable substitution of “absence of prior nephrectomy” with “less than 1 year from initial RCC diagnosis to start of interferon therapy.” Again, based on the five variables, patients were stratified into low-, medium-, and high-risk groups, with a survival of 30, 14, and 5 months, respectively (69). Mekhail et al. (70) validated this model using a sample of 353 previously untreated patients enrolled in clinical trials at the Cleveland Clinic. The median survival times using the MSKCC model in this validation study were 28.6 months for low-risk patients, 14.6 months for intermediate-risk patients, and 5 months for high-risk patients. Two additional independent prognostic factors were identified; namely, prior radiotherapy and sites of metastasis. Incorporating these two variables to include a total of seven variables in the prognostic algorithm, there was further consistency with respect to median survival by risk group in the MSKCC model (70).

To further enhance the applicability of these prognostic models to current clinical trials, Motzer et al. (71) first assessed 251 patients treated in 1975 and 2002 and found that those treated after 1990 had improved survival. Further analysis of the group treated after 1990 allowed for identification of three independent prognostic factors associated with shorter survival; namely, (a) low Karnofsky performance status, (b) low hemoglobin level, and (c) high corrected serum calcium. Stratifying the recently treated patients by these categories allowed for identification of the same three risk groups. Median survival was 22 months in the low-risk group (no risk factors), 11.9 months in the intermediate-risk group (one risk factor), and 5.4 months in patients in the high-risk group (two or three risk factors) (71).

The aforementioned models are limited to metastatic disease, but since then several efforts have been made to define prognosis in localized disease as well. Kattan et al. (72) developed a nomogram based on 601 patients with localized disease treated with nephrectomy. Independent prognostic variables included histologic subtype, symptoms (divided into incidental, local, or systemic), tumor size, and pathologic stage. Comparison of predicted survival using the derived nomogram with the actual patient outcomes suggested reasonable accuracy of the model (area under receiver operating characteristic curve of 0.74) (72).

The Mayo Clinic Experience

To enhance predictive capabilities in the setting of localized disease, the Mayo Clinic explored a much larger database of 1,801 patients with CCRCC. Multivariate analysis yielded an association of survival with TNM stage, tumor size ≥5 cm, nuclear grade, and histologic tumor necrosis. Each parameter was weighted with respect to the associated outcome, and, ultimately, the stage, size, grade, and necrosis (SSIGN) score was derived to mathematically summarize these variables (with total scores ranging from 1 to 10) (73). A recent study by Thompson et al. (74) expanded on the data from this study to establish a score (designated the Dynamic-SSIGN, or D-SSIGN, score) that accounts for a variable disease-free interval after surgery. The D-SSIGN score was generated from an assessment of 1,560 patients treated for localized CCRCC with nephrectomy. SSIGN scores were used
Prognostic Factors in Renal Cell Carcinoma Patients

to stratify patients, and it was noted that patient outcomes improved as the disease-free interval subsequent to surgery increased. For example, those patients with a SSIGN score of 5 had a 5-year cancer-specific survival rate of 69.6%. With an increasing interval of survival after surgery, this period was lengthened, with adjusted 5-year cancer-specific survival of 81.9% at 1 year, 91.9% at 2 years, and 93.2% at 3 years. A similar trend was observed with the entire range of SSIGN scores (74).

The University of California, Los Angeles Experience

Similar to the Mayo Clinic model, the University of California, Los Angeles (UCLA) Integrated Staging System accounts for both localized and metastatic disease. This prognostic model was derived from assessment of 64 combinations of TNM stage, Fuhrman grade, and ECOG-PS data in 661 patients treated with nephrectomy at UCLA (75). Of note, these patients had been treated within the context of 11 clinical trials using IL-2–based therapy. The resulting UCLA Integrated Staging System (UISS) score allowed for stratification of patients into five classes based on these three clinicopathologic variables. Projected 2- and 5-year survival for UISS groups were reported to be 96% and 94% for group I disease, 89% and 67% for group II disease, 66% and 39% for group III disease, 42% and 23% for group IV disease, and 9% and 0% for group V disease (Table 4) (75). The UISS was later modified to include three general prognostic groups designated low, intermediate, and high risk (76).

The UISS prognostic system was validated in the setting of a multicenter study including 4,202 patients from eight international academic centers. The UISS score was used to stratify these patients into low-, intermediate-, and high-risk groups, and 5-year survival in these respective groups in the setting of localized RCC was 92%, 67%, and 44%. Three-year survival for metastatic disease was 37%, 23%, and 12% based on the same stratification (Figure 2). Of note, the predictive value of the UISS score was diminished to some extent in the metastatic setting, and a greater variability in survival was found among centers when applying the score to high-risk patients. The authors posit that this may have been the result of greater heterogeneity in both patient-related variables and treatments applied to these groups (77).

Future Directions

These studies provide evidence that a number of clinicopathologic variables, including TNM stage, Fuhrman grade, and histologic subtype, demonstrate significant correlation with various measures of outcome. The different integrated staging systems presented provide a concise manner in which these correlations can be interpreted to provide prognostic information to the patient and to guide further decision making for adjuvant therapy. Additionally, a great deal of evidence has been presented regarding molecular correlations that exist in patients with RCC (Table 5). Given the advent of numerous targeted therapies with
Table 4. The UISS categorization of 1997 TNM stage, Fuhrman grade, the ECOG-PS, and associated 2- and 5-year survival

<table>
<thead>
<tr>
<th>UISS</th>
<th>1997 TNM stage</th>
<th>Fuhrman grade</th>
<th>ECOG-PS</th>
<th>2-year survival %</th>
<th>SE</th>
<th>5-year survival %</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>1, 2</td>
<td>0</td>
<td>96</td>
<td>2.5</td>
<td>94</td>
<td>2.5</td>
</tr>
<tr>
<td>I</td>
<td>I</td>
<td>1, 2</td>
<td>1 or more</td>
<td>89</td>
<td>3.8</td>
<td>67</td>
<td>6.4</td>
</tr>
<tr>
<td>I</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>1 or more</td>
<td>1 or more</td>
<td>66</td>
<td>6.5</td>
<td>39</td>
<td>2.8</td>
</tr>
<tr>
<td>IV</td>
<td>1, 2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3, 4</td>
<td>0</td>
<td></td>
<td>42</td>
<td>3.5</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>V</td>
<td>1–3</td>
<td>1 or more</td>
<td></td>
<td>9</td>
<td>6.2</td>
<td>0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

ECOG-PS = Eastern Cooperative Oncology Group performance status; SE = standard error; TNM = tumor, node, metastasis; UISS = University of California, Los Angeles Integrated Staging System.

Figure 2. Survival estimates as per the University of California, Los Angeles Integrated Staging System in 3,119 (A) and 1,083 (B) patients with localized and metastatic disease. HR = high risk; IR = intermediate risk; LR = low risk. (From Patard JJ, Kim HL, Lam JS, et al. Use of the University of California Los Angeles Integrated Staging System to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 2004;22:3316–3322, with permission.)
proven efficacy for RCC, it is likely that the inclusion of molecular variables in integrated staging systems will occur more frequently. This is exemplified in a study by Pantuck et al. (59) that examines the components involved in the PI3K-Akt-mTOR pathway as a means of predicting prognosis. The study used paraffin-embedded specimens from 375 patients treated with nephrectomy for RCC. Immunohistochemical analysis of signal cascade members, including cytoplasmic pAkt, nuclear pAkt, PTEN, cytoplasmic p27, and pS6, was per-

<table>
<thead>
<tr>
<th>Category</th>
<th>Related prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic features</td>
<td>Tumor size</td>
</tr>
<tr>
<td></td>
<td>Adrenal extension</td>
</tr>
<tr>
<td></td>
<td>Fatty tissue invasion</td>
</tr>
<tr>
<td></td>
<td>Venous involvement</td>
</tr>
<tr>
<td></td>
<td>Lymph node involvement</td>
</tr>
<tr>
<td>Metastatic disease features</td>
<td>Presence of bony metastases</td>
</tr>
<tr>
<td></td>
<td>Number of metastatic sites</td>
</tr>
<tr>
<td>Histologic features</td>
<td>Fuhrman grade</td>
</tr>
<tr>
<td></td>
<td>Clear cell versus non–clear cell</td>
</tr>
<tr>
<td></td>
<td>Papillary RCC subtype</td>
</tr>
<tr>
<td></td>
<td>Tumor necrosis</td>
</tr>
<tr>
<td></td>
<td>Collecting system invasion</td>
</tr>
<tr>
<td></td>
<td>Sarcomatoid features</td>
</tr>
<tr>
<td></td>
<td>Microvascular invasion</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Eastern Cooperative Oncology Group performance status</td>
</tr>
<tr>
<td></td>
<td>Cachexia-related findings</td>
</tr>
<tr>
<td></td>
<td>Thrombocytosis</td>
</tr>
<tr>
<td>Molecular features</td>
<td>Hypoxia-inducible transcription factor-1a expression</td>
</tr>
<tr>
<td></td>
<td>von Hippel-Lindau gene mutation or hypermethylation</td>
</tr>
<tr>
<td></td>
<td>Carbonic anhydrase IX expression</td>
</tr>
<tr>
<td></td>
<td>Vascular endothelial growth factor expression</td>
</tr>
<tr>
<td></td>
<td>Loss of phosphatase and tensin homolog (PTEN)</td>
</tr>
<tr>
<td></td>
<td>Cellular localization of p21</td>
</tr>
<tr>
<td></td>
<td>Level of p21 expression</td>
</tr>
<tr>
<td></td>
<td>Interleukin-4 promoter mutations</td>
</tr>
</tbody>
</table>

*In patients receiving interleukin-2 therapy.*
formed. Multivariate analysis in this study used both clinical and pathologic features, with ECOG-PS, TNM classification, cytoplasmic Akt, nuclear pAkt, PTEN, and pS6 being identified as independent prognostic factors related to disease-specific survival (59). Presumably, molecular therapies targeting the mTOR receptor (e.g., temsirolimus) should have enhanced activity in the setting of PI3K-Akt-mTOR pathway overactivity.

Accommodation of targeted therapeutics in current algorithms is an ongoing effort. Sunitinib, an orally administered inhibitor of VEGFR and platelet-derived growth factor receptor, was compared to IFN-α in a recent randomized phase III trial of 750 patients with metastatic CCRCC. The study demonstrated an improvement in median progression-free survival with sunitinib (11 months vs. 5 months; \( P < .001 \)), and a higher objective response rate (31% vs. 6%; \( P < .001 \)) (78). Review of baseline characteristics of the population and correlation with outcome seemed to suggest that the MSKCC prediction model for outcome was applicable to patients receiving sunitinib therapy (69,79). Specifically, baseline features found to be predictive of longer progression-free survival included hemoglobin above the lower limit of normal, ECOG-PS score of 0, corrected calcium \( \leq 10 \) mg/dL, and time from diagnosis to treatment of <1 year (79).

As anticipated, data are also emerging to suggest the utility of molecular markers in predicting therapeutic responses of targeted agents. Choueiri et al. (80) recently presented preliminary results from a retrospective analysis of 143 patients treated with VEGF-targeted therapy (including the tyrosine kinase inhibitors sunitinib, sorafenib, and axitinib, and the monoclonal antibody bevacizumab). Patients with VHL gene mutations had an overall response rate of 46%, compared to 28% in those without mutations. The presence or absence of VHL mutations remained an independent prognostic factor for response even after consideration of several clinical prognostic factors, including ECOG-PS, anemia, calcium level, prior therapy, and number of metastatic sites (80).

Studies such as this should prompt a great deal of inquiry into the incorporation of molecular features of RCC in prognostic models. In the same manner as the increasing use of immunotherapies altered prognostic models of RCC a decade ago, targeted therapies will likely warrant modification of the current prognostic schemes. Still, the integrated staging systems that have been derived thus far will serve as a paradigm for developing such algorithms in the future.

References


Advanced Clear Cell Carcinoma: Immunologic Characteristics and Results with Vaccines and Cytokines

Guru Sonpavde, MD, and Thomas E. Hutson, DO, PharmD, FACP

Immunotherapy with cytokines (interferon [IFN] and interleukin-2 [IL-2]) has been the mainstay of therapy for advanced clear cell renal cell carcinoma (CCRCC) until very recently. Notwithstanding the improved outcomes demonstrated by targeted therapy (sunitinib malate, sorafenib tosylate, bevacizumab, and temsirolimus), these agents do not produce complete remissions (CR) or cures (1–4). At present, high-dose (HD) IL-2 remains the only therapy for advanced RCC that has the potential to produce durable CRs and apparent cures, albeit in a small proportion of highly selected patients. Vaccines have been demonstrated to generate tumor-specific immune responses and are emerging as tolerable and effective targeted therapy. Therefore, immunotherapy continues to be an important part of the therapeutic armamentarium and deserves further development. In this chapter, we review the immunologic characteristics of CCRCC and results with cytokines and vaccines.

Biologic Basis of Immunotherapy for Renal Cell Carcinoma

Based on reports of spontaneous regression of metastatic lesions (5), the presence of cytotoxic T lymphocytes in renal tumors (6), the reports of prolonged stable disease in the absence of systemic therapy (7), and the recent descriptions of tumor-associated and HLA-restricted antigens on renal cancer cells, immunologic approaches to the therapy of this tumor are reasonable. The major approaches used have included cytokines as single agents or in combination with chemotherapy and adoptive therapy. The therapeutic effects of natural and recombinant cytokines have been investigated since the 1980s. Two agents, IL-2
and IFN-α, appear to produce tumor regressions in 10%–15% of patients in a reproducible fashion. Other cytokines have been investigated in metastatic RCC; however, their antitumor activity has not been consistently demonstrated.

**Interleukin-2**

First described in 1976 by Morgan et al. (8), IL-2 is a T-cell growth factor with strong immunoproliferative and immunomodulatory properties activating subsets of nonspecific cytotoxic T and natural killer cells in vivo (9). IL-2 was initially used for the treatment of metastatic RCC in 1984 after in vitro and animal studies demonstrated its significant activity as an antitumor agent. Since then, this cytokine has been extensively tested in RCC patients at both low (10) and high doses (11), both as monotherapy and in combination with other agents (12). In general, monotherapy of metastatic RCC using recombinant IL-2 has demonstrated efficacy roughly equivalent to that of monotherapy with recombinant IFN-α (12). The combined response rates (complete and partial), range from 0% to 31%. A review of published clinical studies using IL-2 as systemic therapy for metastatic RCC revealed an objective tumor response of 14% (12). The U.S. Food and Drug Administration approved HD IL-2 in 1992 for the treatment of metastatic RCC, and it became the first biologic to be approved for this disease.

Clinical trials evaluating HD IL-2 therapy in RCC have reported variable objective tumor responses (12). Complete responses to this therapy range from 0% to 13% of treated patients, whereas partial responses (PRs) range from 0% to 30% of patients. The toxicity of bolus intravenous IL-2 depends on the dose used. A flu-like syndrome that includes fever, chills, and myalgias is experienced by most patients. Cardiovascular, pulmonary, and central nervous system toxicity are associated with HD IL-2 (13). Cardiovascular toxicity includes hypotension requiring vasopressors, cardiac arrhythmias, myocardial infarction, and myocarditis. Pulmonary toxicity secondary to capillary leak syndrome may develop and require mechanical ventilation. Grade 3 renal toxicity with oliguria, can occur in more than 20% of treated patients, with creatinine levels over 8 mg/dL reported in 2%. Confusion and neuropsychiatric complaints are also common. Careful patient selection is required to minimize the morbidity and mortality associated with administration of HD IL-2. Recent guidelines for the management of HD IL-2 toxicity have been developed (14). Due to the significant toxicity from HD IL-2 therapy, alternative low-dose (LD) regimens have been developed and studied in patients with metastatic RCC.

In an attempt to help clarify the role of HD and LD IL-2 regimens for the treatment of patients with metastatic RCC, two randomized trials have been conducted. Yang et al. (15) reported the results of a randomized trial to determine the effectiveness of subcutaneous (SC) IL-2 (94 patients) compared with LD (150 patients) and HD bolus IL-2 (156 patients) in a total of 400 patients with metastatic RCC. There was a higher response rate with HD IL-2 (21%) versus LD IL-2 (13%; \( P = .048 \)) but no overall survival (OS) difference. The response rate of SC IL-2 (10%, partial and complete response) was similar to that of LD IL-2. Response
durability and survival in completely responding patients was superior with HD IL-2 compared to LD IL-2 therapy (P = .04). As expected, toxicities were significantly less frequent with both LD IL-2 and SC IL-2, especially hypotension. The second trial, conducted by the Cytokine Working Group and reported by McDermott et al. (16), randomized 192 patients with metastatic RCC to receive either outpatient SC IL-2 and SC IFN-α combination therapy (96 patients) or HD IL-2 (96 patients) therapy. The response rate was 23.2% (22 of 95 evaluable patients) for HD IL-2 versus 9.9% (9 of 91 evaluable patients) for the combination of SC IL-2 and SC IFN-α. Ten patients receiving HD IL-2 were progression free at 3 years compared to three patients receiving combination therapy, and the median survival favored HD IL-2 although was not statistically significant. In this study, patients with bone or liver metastasis and primary tumor in place had a superior survival with HD IL-2 (P = .040). Neither study has demonstrated a clear survival advantage to HD IL-2 therapy, although objective tumor responses and the durability of response in complete responders appear to be improved.

In summary, IL-2 therapy for metastatic RCC yields objective responses in a minority of patients, but with durable efficacy (≥5 years) achieved in patients with complete response to therapy. The superiority of HD IL-2 therapy for significantly increasing survival in patients with metastatic RCC has not been validated due to the lack of randomized studies comparing IL-2 directly with other therapies. The use of surrogates for response to HD IL-2 is intriguing and may help identify patients more likely to respond to this therapy. Controlled, randomized studies of IL-2 therapy for RCC are needed to clarify its therapeutic benefit for the treatment of metastatic disease, especially with the development of novel targeted agents with significantly less toxicity and greater activity.

**Predictors of Response to Interleukin-2**

Several clinical factors have recently been described in patients with RCC receiving cytokine-based therapy (17,18). Factors predictive of rapid progression under cytokine treatment include the presence of hepatic metastases, a short interval from renal tumor to metastases (<1 year), the presence of more than one metastatic site, and elevated neutrophil counts (17,18). RCC response to IL-2 therapy and patient survival has been correlated to histology (clear cell and alveolar features) (19), as well as carbonic anhydrase IX (CA IX G250 antigen) expression (20). Retrospective analysis of paraffin-embedded tissue sections of RCC from 66 patients enrolled in a previously reported Cytokine Working Group trial (21) demonstrated high CA IX expression in 78% (21 of 27) patients who responded to HD IL-2 therapy compared to only 51% (20 of 39) patients who did not respond to therapy. In this study, the percentage of CA IX positive tumor cells was used to separate high (>85%) versus low (≤85%) expressers. When combining good and intermediate pathology, as defined by Upton et al. (19), with high expression of CA IX, the resultant group contained 96% of responders to HD IL-2 therapy compared to only 46% of nonresponders. Prospective study of CA IX expression as a surrogate to predict response to HD IL-2 therapy is ongoing. In a separate analysis, Pantuck et al. were able to identify a set of 73 genes
Advanced Clear Cell Carcinoma

whose expression distinguished complete responders from nonresponders after IL-2 therapy (22). Complete responders to IL-2 have a signature gene and protein expression pattern that includes CA IX, PTEN, and CXCR4. Although this approach also requires prospective validation, it may become a powerful aid to select appropriate treatment options.

Future Development of Interleukin-2 Therapy

The Cytokine Working Group recently launched the HD IL-2 “Select” Trial. The primary objective of this study is to prospectively determine if the aforementioned predictive model (baseline immune function, immunohistochemical markers, and gene expression patterns) can identify patients with advanced RCC more likely to respond to HD IL-2 than a historical, unselected patient population (20). Although adjuvant cytokine therapy with either IFN-α or HD IL-2 or combination chemoimmunotherapy (LD IL-2 plus IFN-α plus fluorouracil) has also not yielded globally improved outcomes, optimal patient selection may yield enhanced outcomes (23–25). Combination of HD IL-2 with antiangiogenic agents and other immunotherapeutic modalities is being explored (Table 1).

Interferon, Pegylated Interferon, and Other Cytokines

The antitumor activity of IFN in patients with RCC was first reported in 1983 by two groups of investigators (26,27). The actual mechanisms responsible for the antitumor activity of IFN in human cancer remain uncertain. Possible mechanisms may include inhibition of oncogene function (28) and enhancement of immune regulatory actions, including effector cell cytolytic activity and expression of class II major histocompatibility complex proteins on cell surfaces (28). The most commonly used preparations in clinical practice are recombinant IFN-α2a (Roferon A®, Hoffman-LaRoche, Nutley, NJ) and recombinant IFN-α2b (IntronA®, Schering-Plough Laboratories, Kenilworth, NJ). Both have been studied extensively in patients with metastatic RCC in doses ranging from 3 MU (million units) to 50 MU per day. Response rates range from 0% to 30% (12), and the overall response rate is 14.5% (13 complete and 81 PR; 95% confidence interval [CI] 12%–17%) in 648 patients (12). Optimal results appear to be associated with doses from 5 to 10 MU/m² (29). Responses occur most frequently in patients with pulmonary metastases and good performance status (30,31). Median response duration is generally between 6 and 10 months, but, occasionally, durable complete regressions over 2 years are seen (31).

In an attempt to further define the role of cytokines as treatment for metastatic RCC of intermediate prognosis (≥1 metastatic site; ≥1 year from renal tumor to metastasis), the French Immunotherapy Intergroup conducted a phase III trial and reported the initial results at the American Society of Clinical Oncology meeting in 2005 (32). A total of 456 patients were randomized to medroxyprogesterone acetate (MPA), IFN-α, LD SC IL-2, and the combination of IFN-α and IL-2. The response rates at 3 months in the four treatment groups
were 2.5% (MPA), 4.4% (IFN-α), 4.1% (IL-2), and 10.9% (IFN-α and IL-2). Unexpectedly, the overall response rate did not differ between groups (median OS = 15 months; \( P > .05 \)). Although these results would suggest that cytokines should not be used in metastatic RCC patients of “intermediate” prognosis, several concerns regarding the interpretation of these results have been raised: (a) The OS is longer than would be anticipated in
Advanced Clear Cell Carcinoma

this patient population (historical survival in patients with intermediate prognosis is 12–13 months), suggesting that patients may have received additional “active” therapies on progression; (b) there was no comparison to HD IL-2 therapy; and (c) previous clinical trials have shown modest survival benefits with LD cytokines and included a significant proportion of patients with “intermediate” prognostic factors. Nonetheless, this clinical trial does suggest that LD cytokine therapy may not provide significant benefit in patients with less than favorable prognosis, and more effective therapies are needed.

Two randomized trials have demonstrated a statistically significant survival advantage in RCC patients with synchronous metastatic disease who received cytoreductive nephrectomy followed by IFN-\(\alpha\) (33,34). The first trial, reported by the Southwest Oncology Group (33), randomized 246 patients to nephrectomy followed by IFN-\(\alpha\) compared with single-agent IFN-\(\alpha\) without surgery. In the 120 eligible patients undergoing adjunctive nephrectomy followed by IFN-\(\alpha\), improvement in survival was noted (11.1 months vs. 8.1 months; \(P = .05\)). In the second trial, Mickisch et al. (34) randomized 85 patients to nephrectomy followed by IFN-\(\alpha\) or single-agent IFN-\(\alpha\) without surgery. Both time to progression (5 months vs. 3 months; hazard ratio [HR] 0.60; 95% CI 0.36–0.97) and median duration of survival were significantly better in the patients receiving nephrectomy and IFN-\(\alpha\) (17 months vs. 7 months; HR 0.54; 95% CI 0.31–0.94). These trials suggest that patients with primary tumors in place and metastatic disease should be considered for nephrectomy (if medically possible) before IFN-\(\alpha\) therapy. Retrospective reviews of data also suggest this approach can be considered in patients receiving other cytokines such as IL-2 (35).

In two phase III studies, conventional IFN-\(\alpha\) conferred a survival benefit (37). Although a recently reported randomized trial (B017705) demonstrated improved progression-free survival (PFS) for frontline IFN-\(\alpha\) plus bevacizumab compared to IFN-\(\alpha\) alone (10.2 vs. 5.4 months; \(P < .0001\)), the role of IFN-\(\alpha\) in the combination regimen is unclear (4). Besides being proangiogenic, vascular endothelial growth factor (VEGF) appears to suppress immune function (38). Therefore, anti-VEGF therapy with bevacizumab may reverse these immunosuppressive effects. Although IFN-\(\alpha\) has been supplanted by sunitinib malate and temsirolimus, pegylated (PEG) IFN-\(\alpha\) is conveniently administered once weekly and appears similar to IFN-\(\alpha\) in terms of efficacy and may be more tolerable (39,40). Pharmacokinetic data show a lower peak serum concentration and a longer half-life, allowing weekly PEG-IFN-\(\alpha\) (41). It has been argued that the longer half-life may translate into improved efficacy compared with conventional IFN-\(\alpha\) (39). In the absence of randomized trials incorporating PEG-IFN-\(\alpha\), its definitive role in the therapeutic armamentarium is unclear. Other cytokines have been preliminarily investigated, and further studies are ongoing (see Table 1).

Vaccines

Dendritic Cell Vaccines

Dendritic cell (DC) vaccination against cancer is a relatively recent immunotherapeutic approach. The optimal vaccine preparation, administration route, or treatment schedule
remains unclear. Tumor lysates, and peptides combined with DCs of different maturation state, have been evaluated. A total of 183 patients with metastatic RCC were treated with DC vaccination in 15 phase I/II clinical trials (42). Seventy-seven patients (38%) had a clinical response, with four complete and eight PRs, and sixty-one with disease stabilization, whereas four had a mixed response. As expected, DC vaccination resulted in peptide/tumor–specific immune responses, albeit in a subset of patients. In some patients, there was epitope spreading (i.e., T-cell responses to antigens not used for vaccination). Further studies with DC vaccines are ongoing (Table 2).

**Viral Vector–Based Vaccines**

RCC appears to have high levels of 5T4 expression, which suggests that these patients could benefit from a 5T4-targeted product such as TroVax® (Oxford BioMedica, Oxford, UK) (42). TroVax® consists of an attenuated poxvirus that delivers the 5T4 gene and elicits an immune response against 5T4. An ongoing trial is evaluating this vaccine (see Table 2).

**Tumor Cell–Based Vaccines**

Vaccines were moved into the adjuvant setting in the hope that lesser disease burden would enhance efficacy. A total of 558 patients with a renal tumor >2.5 cm were enrolled preoperatively for adjuvant tumor cell–based vaccine versus no adjuvant therapy after radical nephrectomy (44). Of these patients, 174 were withdrawn because they did not fulfill inclusion criteria or ability to prepare a vaccine. Only 379 patients were assessable for the intention-to-treat analysis. At 5-year and 70-month follow-up, the HRs for tumor progression were 1.58 and 1.59, respectively, in favor of the vaccine group \( (P = .0204) \). Five-year and 70-month PFS rates were 77.4% and 72%, respectively, in the vaccine group and 67.8% and 59.3%, respectively, in the control group. The vaccine was well tolerated, with only 12 adverse events.

**Heat-Shock Protein-Peptide Complex Vaccine**

Vaccination with autologous heat-shock protein (HSP)-peptide (Oncophage®) complexes produced from each patient’s tumor has been investigated in early-stage, high-risk RCC (T2–T4 or node-positive disease) compared to no therapy in a phase III trial (45). Surgically removed tumor tissue was processed to capture the HSP-peptides, which are then purified. The primary end point was recurrence-free survival (RFS), with OS being the secondary end point. Of the 728 patients entered, data review indicated that 124
Table 2. Selected recently reported and ongoing vaccine trials

<table>
<thead>
<tr>
<th>Institution</th>
<th>Eligibility</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Vaccine</th>
<th>Control</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Adjuvant</td>
<td>Adjuvant high-risk localized</td>
<td>III</td>
<td>Industry</td>
<td>Oncophage</td>
<td>Observation</td>
<td>Preliminarily, no overall improvement in PFS</td>
</tr>
<tr>
<td>German</td>
<td>Adjuvant high-risk localized</td>
<td>III</td>
<td>Industry</td>
<td>Autologous tumor lysate</td>
<td>Observation</td>
<td>Improved 5-yr and 70-mo PFS</td>
</tr>
<tr>
<td>Multi-site combined phase II data</td>
<td>Metastatic</td>
<td>II</td>
<td>Variable</td>
<td>Dendritic cell</td>
<td>—</td>
<td>38% responding or stable disease</td>
</tr>
<tr>
<td>International (TroVax Renal Immunotherapy Survival Trial)</td>
<td>Metastatic</td>
<td>III</td>
<td>Industry</td>
<td>TroVax® + standard of care (e.g., sunitinib)</td>
<td>Placebo + standard of care</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Columbia University</td>
<td>Metastatic</td>
<td>II</td>
<td>Industry</td>
<td>TroVax® + high-dose interleukin-2</td>
<td>—</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Hoag Cancer Center</td>
<td>Metastatic</td>
<td>II</td>
<td>Other</td>
<td>Autologous tumor and dendritic cells</td>
<td>—</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Multicenter</td>
<td>Metastatic</td>
<td>I/II</td>
<td>Industry</td>
<td>Dendritic cells pulsed with tumor and CD40</td>
<td>—</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCI</td>
<td>Metastatic</td>
<td>II</td>
<td>NCI</td>
<td>Autologous tumor mutated von Hippel-Lindau peptides</td>
<td>—</td>
<td>Pending</td>
</tr>
</tbody>
</table>

NCI = National Cancer Institute; PFS = progression-free survival.
Advanced Clear Cell Carcinoma

(17%) were ineligible, as they had disease present at baseline. When the 604 eligible patients were analyzed, RFS was not statistically different between the arms. An ad hoc hypothesis-generating analysis demonstrated a significant improvement in RFS of approximately 45% ($P < .01; HR = 0.55$) and a trend toward improved survival in a subset of intermediate-risk patients ($N = 362$).

Other Modalities of Immunotherapy

Immunomodulatory monoclonal antibodies, adoptive T lymphocyte transfer, and allogeneic hematopoietic stem cell transplantation are currently being studied as therapies for metastatic RCC. WX-G250 is an immunoglobulin G monoclonal antibody targeting CA IX. WX-G250 administered to 36 metastatic RCC patients in a phase II trial was well tolerated and induced stabilization in 11 patients and responses in 2 patients (46). A randomized placebo-controlled phase III trial (ARISER study [Adjuvant Rencarex® Immunotherapy phase III trial to Study Efficacy in non-metastatic RCC]) is evaluating WX-G250 for the adjuvant therapy of resected, localized, high-risk CCRCC. Ipilimumab, an anti-CTLA-4 human monoclonal antibody, yielded modest activity in a phase II trial (47). In 98 of 128 evaluable patients from European sites who underwent allogeneic transplantation, 28 objective responses (32%) were observed (4 CRs and 24 PRs) (48). The treatment-related mortality was 16% at 1 year. Tumor responses were associated with acute graft-versus-host disease (GVHD), HLA-mismatched donor, and <1-year period from diagnosis of metastatic disease to transplantation. Survival was associated with chronic GVHD, donor lymphocyte infusion after transplantation, and <3 metastatic sites.

Summary

In aggregate, these studies suggest that HD IL-2 is the only modality demonstrated to potentially cure some patients with CCRCC. However, given the toxicity and limited efficacy of HD IL-2 therapy, additional efforts should be directed at better defining the patient population for whom this therapy is appropriate. Data suggest that patients with good or intermediate prognosis features, prior nephrectomy, clear cell histology (especially alveolar features and the absence of papillary or granular features), high CA IX expression, and specific genomic signatures are more likely to benefit from HD IL-2 therapy. The role of IFN as a therapy for RCC has been revitalized based on the results of the phase III AVOREN trial demonstrating a statistically significant PFS benefit to the combination of bevacizumab and IFN, although the contribution of IFN to this regimen is uncertain. Vaccines and other forms of immunotherapy are emerging as tolerable and potentially useful additions to the therapeutic armamentarium. In the era of targeted anti-angiogenic therapy for CCRCC, immunotherapy remains an important modality to further develop.
Advanced Clear Cell Carcinoma

Renal cell carcinoma (RCC) is the most common neoplasm of the kidney. The treatment options in this disease have been expanded with the discovery of the VHL (von Hippel-Lindau) gene mutation and the subsequent understanding of the relevance of angiogenic pathways in RCC; therefore, identifying key pathways and developing molecules for their inhibition is a great breakthrough in treating this chemotherapy-resistant cancer. There are three newly approved drugs, sorafenib (Nexavar®), sunitinib (Sutent®), and temsirolimus (Torisel®) in RCC, of which the first two are multi-targeted tyrosine kinase inhibitors (TKIs). AG-013736 (axitinib) and GW-786034 (pazopanib), two agents that have shown activity in RCC, are discussed in this chapter in addition to sunitinib and sorafenib. This chapter focuses on the data and use of sorafenib and sunitinib.

Newly Approved Multikinase Inhibitors in Renal Cell Carcinoma

Sorafenib tosylate and sunitinib malate are both approved for use in the setting of advanced RCC. Even though temsirolimus is not a multi-targeted kinase inhibitor, we briefly discuss it in this chapter. Data from a phase III, randomized, placebo-controlled trial in the treatment of refractory patients demonstrated that sorafenib increased progression-free survival (PFS) to 24 weeks compared with 12 weeks in a placebo-treated
Sorafenib also produced tumor shrinkage in four out of five patients (78%), with a 10% (investigator assessed) RECIST (Response Evaluation Criteria in Solid Tumors) response rate (1). This agent was approved by the U.S. Food and Drug Administration (FDA) on December 20, 2005, for therapy of patients with advanced RCC.

Sunitinib maleate, also a small-molecule TKI, was demonstrated to have significant clinical activity in patients who previously failed cytokine therapy. A sequence of phase II trials demonstrated a 40% partial response (PR) rate, with a median time to tumor progression of 8.7 months (2,3). This agent was approved (accelerated approval) in view of the high response rate in the setting of an unmet need for therapy of metastatic RCC based on these studies. A recently published phase III trial in treatment of naïve patients confirmed the response rate and demonstrated an increase in PFS from 5.0 to 11.0 months when compared to interferon-α (IFN-α).

**Sorafenib**

Sorafenib (Nexavar®) is a water-insoluble tosylate salt, with a molecular weight of 464.825 g/mol. The mean relative bioavailability is 38%-49% for the tablet form as opposed to the oral solution. The bioavailability decreases to 29% with a fatty meal, and 99.5% is protein bound. The half-life of sorafenib is between 25 and 48 hours. Drug metabolism involves the P450 cytochrome system.

Sorafenib is a multi-targeted kinase inhibitor that targets several serine/threonine and receptor tyrosine kinases. Sorafenib targets the intracellular kinases, including CRAF, BRAF, and mutant BRAF. It also inhibits the cell surface kinases such as c-KIT, FLT-3, vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor (PDGFR)-β (4,5). These kinases appear to play an important role in angiogenesis and cellular proliferation (Table 1). Sorafenib may affect tumor cell proliferation by its effects on the Raf/MEK/ERK pathway, as well as angiogenesis inhibition (6). The recommended dosing regimen is 400 mg bid, with dose reductions to 400 mg daily and 400 mg every other day, depending on toxicity. The dose levels of 600 mg bid and 800 mg bid are currently under investigation.

**Phase II Randomized Discontinuation Trial**

The phase I trials were followed by a phase II randomized discontinuation trial in solid tumor patients. This trial included 202 patients with metastatic RCC, of whom 170 had received prior therapy (7), and 32 patients who were treatment naïve. In the open label portion of the study, all patients received 400 mg bid of sorafenib. The analysis of 193 evaluable patients demonstrated 36% (N = 73) had ≥25% decrease in tumor size, 34% stable disease (SD; N = 69), and 25% progressive disease (PD; N = 51), with an overall RECIST response rate of <5%. At week
12, 65 patients with SD were randomized to either continue sorafenib (N = 32) or a placebo (N = 33). Twelve weeks after randomization, 50% (N = 16) of the patients in the sorafenib arm and 18% (N = 6) in the placebo group remained progression free (P = .0077). The median PFS was significantly improved in the sorafenib group (24 weeks) compared to the placebo-arm patients (6 weeks; P = .0087). In the treatment naïve subset, there were 27 evaluable patients, with 6 PRs (18.8%), 18 patients with SD (56.3%), and 3 with PD (9.4%), for a 75% clinical benefit rate (complete response [CR] + PR + SD) (7,8). In this group, the median time to progression (TTP) was 40 weeks. The results in this trial suggested sorafenib had a significant effect in controlling disease progression despite a response rate of ≤10% (in the treatment refractory setting), and a randomized phase III study was subsequently conducted.

### Table 1. Sorafenib targets and the respective concentrations that inhibit 50% (IC$_{50}$)

<table>
<thead>
<tr>
<th>Target</th>
<th>Pathway significance</th>
<th>Sorafenib IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFR</td>
<td>Angiogenesis/RTKs</td>
<td>57 ± 20 nmol/L</td>
</tr>
<tr>
<td>PDGFR-α</td>
<td>Angiogenesis/RTKs</td>
<td>NA</td>
</tr>
<tr>
<td>Fibroblast growth factor receptor 1</td>
<td>Angiogenesis/RTKs</td>
<td>90 ± 5 nmol/L</td>
</tr>
<tr>
<td>VEGFR-1</td>
<td>Angiogenesis/RTKs</td>
<td>NA</td>
</tr>
<tr>
<td>Flk-1-KDR or VEGFR-2</td>
<td>Angiogenesis/RTKs</td>
<td>20 ± 6 nmol/L</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>Angiogenesis/RTKs</td>
<td>68 ± 21 nmol/L</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Stem cell factor receptor</td>
<td>6 ± 3 nmol/L</td>
</tr>
<tr>
<td>Raf-1</td>
<td>Cellular proliferation/signal transduction</td>
<td>22 ± 6 nmol/L</td>
</tr>
<tr>
<td>RAF wild</td>
<td>RAS pathway/intracellular signaling receptors</td>
<td>38 ± 9 nmol/L</td>
</tr>
<tr>
<td>RAF mutant</td>
<td>RAS pathway/intracellular signaling receptors</td>
<td>58 ± 20 nmol/L</td>
</tr>
<tr>
<td>FLT-3</td>
<td>Fms-like tyrosine kinase</td>
<td>NA</td>
</tr>
<tr>
<td>c-RET</td>
<td>RET signaling pathways/stress response pathway</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available; PDGFR = platelet-derived growth factor receptor; RTKs = receptor tyrosine kinases; VEGFR = vascular endothelial growth factor receptor.
Phase III Placebo-Controlled Trial
The phase III placebo-controlled trial (TARGETs) evaluating sorafenib in treatment-refractory patients randomized 903 individuals with clear cell carcinoma to receive either sorafenib (N = 451) or a placebo (N = 452) (9,10). The primary end point was overall survival (OS), and secondary end points were PFS and response. The first interim analysis demonstrated a significant improvement in PFS for sorafenib-treated patients compared with those receiving a placebo (24 vs. 12 weeks; hazard ratio [HR] = 0.44; P <.000001) (1). After this, patients were permitted to cross over from placebo to sorafenib. A prespecified interim analysis of OS, using a stratified log-rank test, was performed 6 months after the crossover was initiated, and 216 of 452 placebo patients had crossed over to sorafenib. The median OS for sorafenib patients was 19.3 months and 15.9 months for the placebo group (HR = 0.77; 95% confidence interval [CI]: 0.63, 0.95; P = .015; level of significance required α = 0.009). After censoring the crossover patients, the median OS for the placebo group was 14.3 months (HR = 0.74; 95% CI: 0.58, 0.93; P = .010), suggesting a potential effect of crossover (Table 2). The final analysis of OS demonstrated an improvement of 13.5% for sorafenib versus placebo (median, 17.8 vs. 15.2 months; HR = 0.88; P = .146; α = 0.037), but this was not significant (11). A preplanned secondary analysis censoring placebo patients showed an OS benefit for sorafenib versus placebo (HR = 0.78; 95% CI: 0.62, 0.97; P = .0287; α = 0.037), confirming that crossover had confounded OS analysis. The PFS benefit seen was independent of prior use of cytokines, age, Memorial Sloan-Kettering Cancer Center (MSKCC) score, presence or absence of lung or liver metastases, and time to diagnosis. Subset analysis of the sorafenib-treated patients, with or without cytokine therapy, demonstrated the PFS was similar in the group that received prior cytokine therapy (24 weeks; HR = 0.54; 95% CI: 0.45, 0.64) and in the group with no prior cytokine treatment (25 weeks; HR = 0.48; 95% CI: 0.32, 0.73)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OS at crossover</th>
<th>OS at 6 mo post-crossover</th>
<th>OS at 6 mo post-crossover, placebo censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo OS</td>
<td>14.7 mo</td>
<td>15.9 mo</td>
<td>14.3 mo</td>
</tr>
<tr>
<td>Sorafenib OS</td>
<td>Not reached</td>
<td>19.3 mo</td>
<td>19.3 mo</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.72</td>
<td>0.77</td>
<td>0.74</td>
</tr>
<tr>
<td>P-value</td>
<td>.018</td>
<td>.015</td>
<td>.01</td>
</tr>
<tr>
<td>O’Brien Fleming</td>
<td>0.0005</td>
<td>0.0094</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available; OS = overall survival.
Another subgroup analysis investigating the effects of age was conducted (<65 years vs. ≥65 years) (13). It was noted that the PFS in patients <65 years (23.9 vs. 12 weeks [HR = 0.61; 95% CI: 0.50, 0.74]) and ≥65 years (25.9 vs. 11.9 weeks [HR = 0.37; 95% CI: 0.27, 0.51]) for the sorafenib versus placebo arms were similar.

The overall response rates at the May 2005 cutoff in the sorafenib arm (N = 451) were 1 CR (<1%), 43 PRs (10%), 333 SD (74%), and 56 PD (12%). In the placebo arm (N = 452), there were 8 PRs (2%), 239 SD (53%), and 167 PD (37%). Disease control rates (SD + PR + CR) in younger versus older patients in the sorafenib group were 60.7% and 64.4%, respectively, and 38% in the placebo group. The findings were consistent with benefit from sorafenib independent of age.

The major adverse events (AEs) were diarrhea, rash, fatigue, and hand–foot reactions (palmo-plantar erythrodysesthesia [Figure 1; Table 3]). Treatment discontinuation due to AEs was reported in 10% of patients receiving sorafenib and 8% receiving the placebo. The principal events responsible for discontinuation were constitutional, gastrointestinal, dermatologic, or pulmonary. Dose reduction was required in 13% of sorafenib-treated patients and 3% of patients in the placebo group (P = .001). Dose interruption was required in 21% of patients in the sorafenib group (mostly for

Figure 1. Palmo-plantar erythrodysesthesia (hand–foot syndrome). This is an example of grade 3 hand–foot syndrome in a patient treated with sorafenib.
Multi-Targeted Kinase Inhibitors in RCC

Table 3. Adverse events seen in the TARGETs trial

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Sorafenib (N = 451)</th>
<th>Placebo (N = 452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>37 (5)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43 (2)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (&lt;1)</td>
<td>19 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (4)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>30 (6)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>40 (1)</td>
<td>16 (&lt;1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27 (&lt;1)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (&lt;1)</td>
<td>6 (0)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>13 (&lt;1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (3)</td>
<td>7 (4)</td>
</tr>
</tbody>
</table>


palmo-plantar erythrodysesthesia/rash/diarrhea) and 6% in the placebo group (P = .001). Cardiac toxicities included hypertension and ischemia. All-grade hypertension was observed in 17% of patients, with 4% having grade 3 toxicity while taking sorafenib, whereas only 2% had all-grade hypertension in the placebo arm. Cardiac ischemia was observed in 12 patients taking sorafenib (3%) and <1% taking placebo. Hypertension was managed by dose interruption per protocol for grade 3 toxicity in addition to the use of appropriate antihypertensives. Only <1% required permanent discontinuation of sorafenib.

This study clearly demonstrated the effects of sorafenib on disease stabilization, with >75% of patients developing measurable tumor shrinkage. The significant increase in PFS for sorafenib-treated patients is consistent with these findings. An example of a patient with tumor shrinkage in response to sorafenib is illustrated in Figure 2. The high disease control rate is mostly attributable to the predominance of SD in the sorafenib-treated patients. SD is defined as the range of tumor volume from −30% to +20%. Figure 3 clearly shows that there are at least 51% of patients who had some sort of tumor shrinkage and another subset of patients who had SD but no tumor shrinkage or experienced increase in tumor volume. Often, the tumors undergo necrosis, as evidenced by the computed axial tomography (CAT) scan images showing varying Hounsfield units in different parts of the tumor (Figure 4). The center of the tumor undergoing necrosis is very common, with or without tumor shrinkage, but this is seen only after initiation of treatment. It has been suggested that a majority of patients with SD had this type of response to sorafenib therapy and not RECIST responses. This reiterates the need to improve the response evaluation in
RCC patients treated with agents such as sorafenib. So the use of RECIST poses a potential for underestimating the biologic effects of TKIs on tumor size and density.

**Phase II Interferon versus Sorafenib**

A phase II trial was conducted in the treatment-naive patients with metastatic clear cell carcinoma (14). One hundred eighty-nine untreated patients were stratified based on MSKCC prognostic score and randomly assigned to receive sorafenib, 400 mg bid (N = 97), or IFN, 9 MU tiw (N = 91) in part 1. PFS was the primary objective in this study. Dose escalation of sorafenib to 600 mg bid on progression (part 2) was permitted, and crossover to sorafenib for IFN-α patients was also included. Preliminary toxicity data demonstrated that the sorafenib arm had more ≥ grade 3 toxicity, including diarrhea (24.7%), hypertension (13.4%), and hand–foot syndrome (6.2%), and, in the control, the IFN arm had a higher incidence of ≥ grade 3 fatigue (20.9%), fever (18.7%), nausea (13.2%), and flu-like syndrome (6.6%). Drug discontinuation was required in 11% of the sorafenib group and 15% of the IFN group due to AEs (15). A final analysis of this trial was completed recently, and the PFS in the sorafenib arm was 5.7 months (CI: 5.0–7.4 months) and in the IFN arm, 5.6 months (CI: 3.7–7.4 months) (15). The progression-free rates for sorafenib versus IFN were 90% versus 70.4%, 45.9% versus 46.5%, and 11.5% versus 30.4% at 3, 6, and 12 months, respectively.

In part 2, on crossover to sorafenib from IFN, the PFS was 5.3 months (N = 50; CI: 3.6–6.1 months). The dosage of 600 mg bid was well tolerated, and the median PFS in this group was 3.6 months (N = 44; CI: 1.9–5.3 months). The primary end point was not
met by this study, but sorafenib demonstrated activity in the front-line setting. PFS benefit was also demonstrated in patients who crossed over from IFN to sorafenib, attesting to its ability to show response in the second-line setting after treating with IFN.

**Phase IV ARCCS Trial**

The Advanced Renal Cell Carcinoma Sorafenib Study (ARCCS) trial was a large expanded access program for therapy of patients with advanced RCC (16,17). This was an open-label, noncomparative phase IV study of sorafenib, and included 1,239 previously untreated patients and 1,249 treatment-refractory patients. The majority of patients had clear cell histology (78%), with 7% having papillary carcinoma. The most common sites of metastases observed were lung (68.2%), kidney (27.4%), bone (26.8%), and liver (23.1%). Eighty-one percent of patients had prior nephrectomy, 821 (35.1%) had prior radiotherapy, and the median time from diagnosis was 1.4 years, with 51.6% of patients having received some sort
of prior therapy. Toxicity included diarrhea (16.3%), rash/desquamation (15.8%), fatigue (13.2%), hand–foot syndrome (10.5%), and hypertension (9.7%). Out of the 2,488 patients who were evaluable for toxicity, grade 3 AEs were reported in <2%. Response was assessed in 1,850 patients (921 front-line patients). RECIST responses included 1 CR (<1%), 67 PRs (4%), 1,479 SD (80%), and 303 PD (16%). This translated into 84% clinical benefit rate/disease control rate. Common grade 3 AEs included hand–foot syndrome (7.2%), rash (4%), fatigue (5.3%), hypertension (4.4%), dehydration (2.7%), dyspnea (2.7%), and diarrhea (2.5%). There were 713 (30.5%) drug-related grade 3 or 4 AEs, 672 (28.8%) serious AEs, and 396 (16.9%) AEs leading to drug discontinuation.

**Sunitinib**

Sunitinib is a malate salt, with a molecular weight of 532.6 d. Sunitinib (Sutent), another small-molecule receptor TKI, inhibits multiple targets including c-KIT, FLT-3, PDGF-α, PDGF-β, and VEGFR-2 (Table 4) (18). Its bioavailability is not affected by food intake. The terminal half-life of sunitinib and its primary active metabolite is 40–60 hours and 80–110 hours, respectively.

![Figure 4. Example of central necrosis in the tumor of a patient treated with sorafenib. The left adrenal mass has necrosed in the center, with a rim of activity in the periphery (arrow) in response to sorafenib after two cycles.](image-url)
Multi-Targeted Kinase Inhibitors in RCC

The metabolism is primarily via the cytochrome P450 system (CYP3A4). The recommended dosage is 50 mg daily for 4 weeks on and 2 weeks off in a 6 week cycle. The treatment break of 2 weeks is required because of toxicity. Dose may be changed as increments or decrements of 12.5 mg to the daily dose, based on the individual patient tolerability and profile.

Table 4. Sunitinib targets and the respective concentrations that inhibit 50% (IC₅₀)

<table>
<thead>
<tr>
<th>Target Pathway significance</th>
<th>Receptor phosphorylation (µM)</th>
<th>Ligand-dependent proliferation (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFR</td>
<td>Angiogenesis/RTKs</td>
<td>0.01</td>
</tr>
<tr>
<td>PDGFR-α</td>
<td>Angiogenesis/RTKs</td>
<td>ND</td>
</tr>
<tr>
<td>Fibroblast growth factor receptor 1</td>
<td>Pathway/extracellular growth factor</td>
<td>ND</td>
</tr>
<tr>
<td>VEGFR-1</td>
<td>Angiogenesis/RTKs</td>
<td>ND</td>
</tr>
<tr>
<td>Flk-1-KDR or VEGFR-2</td>
<td>Angiogenesis/RTKs</td>
<td>0.01</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>Angiogenesis/RTKs</td>
<td>ND</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Stem cell factor receptor</td>
<td>&lt;30 nmol</td>
</tr>
<tr>
<td>Raf-1</td>
<td>Cellular proliferation/signal transduction</td>
<td>NA</td>
</tr>
<tr>
<td>BRAF wild</td>
<td>RAS pathway/intracellular signaling receptors</td>
<td>NA</td>
</tr>
<tr>
<td>BRAF mutant</td>
<td>RAS pathway/intracellular signaling receptors</td>
<td>NA</td>
</tr>
<tr>
<td>FLT-3</td>
<td>Fms-like tyrosine kinase</td>
<td>250 nmol</td>
</tr>
<tr>
<td>c-RET</td>
<td>RET signaling pathways/ stress response pathway</td>
<td>224 nmol</td>
</tr>
</tbody>
</table>

NA = not available; ND = normal dose; PDGFR = platelet-derived growth factor receptor; RTKs = receptor tyrosine kinases; VEGFR = vascular endothelial growth factor receptor.

**Phase II Trials**

The effects of sunitinib in cytokine-refractory RCC patients were evaluated in a sequence of phase II trials after its phase I results (2). The first multicenter trial enrolled 63 patients with advanced RCC refractory to cytokine therapy, of which 55 (87%) had clear cell histology. Sunitinib monotherapy was administered at a dosage of 50 mg orally (PO) daily for 4 of 6 weeks, with cycles repeated every 6-week cycle. In contrast to sorafenib, RECIST PRs were noted in 40% of the patients (N = 25), with 27% (N = 17) having SD at ≥12 weeks. The median survival was 16.4 months (95% CI: 10.8 to not available) and the median TTP was 8.7 months (95% CI: 5.5–10.7). The second phase II trial showed similar results (3). This trial included 106 RCC patients and involved a similar design, but patients had clear cell histology. Thirty-four percent of patients had PRs (N = 36), 29% had SD (N = 30), and 37% had PD (N = 39). The median PFS was 8.3 months (95% CI: 7.8–14.5). On independent review, the PR rate in the trial was noted to be 25.5% (95% CI: 17.5, 34.9). The results of two trials demonstrated the activity of this agent, which was then approved by the FDA for use in metastatic RCC patients in January 2006. An example of an objective response to sunitinib is illustrated in Figure 5 as an X–Y scatter plot and CAT scan in a patient who was treated with sunitinib for ≥12 months.

**Phase III Trial**

A large randomized phase III trial in untreated RCC patients comparing sunitinib with IFN-α was recently published (19,20). Seven hundred fifty patients were randomized to either sunitinib (N = 375) or IFN-α (N = 375). Sunitinib was administered at a dosage of 50 mg daily for 4 out of 6 weeks. IFN-α was administered subcutaneously, with a maximal dosage of 9 MU tiw (million units three times a week) as the maintenance dose. Response evaluation was conducted using RECIST criteria (investigator assessment as well as independent central review). PR were seen in 44% (95% CI: 39, 49) of patients in the sunitinib arm and 33 patients (11%) in the IFN-α arm (95% CI: 8–15, \(P = .000001\)) (21). SD was noted in 160 patients (48%) in the sunitinib arm and 160 patients (49%) in the IFN-α arm. The primary end point, median PFS, was 11 months (95% CI: 10–12) in the sunitinib arm and 5 months (95% CI: 4–6) in the IFN-α arm (HR = 0.42; 95% CI: 0.32–0.54; \(P = .001\)). More AEs were seen with sunitinib therapy, and the incidence of grade 3 or 4 AE was low in both groups. IFN-α had a higher rate of ≥ grade 3 fatigue compared to sunitinib (12% vs. 7%; \(P = .05\)) (Table 5). Compared to IFN, the sunitinib group had more grade 3 diarrhea (5% vs. none with IFN), hypertension (8% vs. 1%), vomiting (4% vs. 1%), and hand–foot syndrome (5% vs. none; \(P < .05\) for all of the preceding comparisons). Other AEs found with IFN included pyrexia, chills, flu-like illness, and myalgia. Grade 3 or more cytopenias occurred more with sunitinib compared to IFN.

**Sunitinib Expanded Access Trial**

The expanded access trial was a multinational study to assess the real-world efficacy and toxicity of sunitinib in patients who were either ineligible for clinical trials or had prior therapies
Multi-Targeted Kinase Inhibitors in RCC

Patients with poor performance status and presence of brain metastases were also enrolled. The primary end point was to provide sunitinib access to patients who were ineligible for clinical trials or who could potentially benefit from this therapy. Secondary end points were safety, efficacy, OS, TTP, and PFS. Though there was slight variation in the local reassessment policies, RECIST was used for response assessment: 4,470 (goal, 5,000) patients were enrolled as of May 2007, and data were available for 2,341 patients. Safety, treatment duration, and response rate were evaluated on an intention-to-treat basis. Median age was 59 years in the group that had 1,985 patients (84.8%) with Eastern Cooperative Oncology Group (ECOG) performance status 0–1, 2,118 patients (90.5%) with prior nephrectomy, and 2,056 patients (87.8%) with clear cell histology. The frequent sites of metastases were lung (78.6%), bone (35.4%), liver (28%), and brain (7.8%). Seventy-eight percent of patients had prior cytokine therapy, and 7.1% had prior antiangiogenic therapy. The median number of sunitinib treatment cycles was four, with duration of treatment being 5.6 months.

Figure 5. Example of a patient’s tumor shrinkage while taking sunitinib. (A) X-Y scatter plot demonstrating continued efficacy of sunitinib even after eight cycles, which is approximately 1 year. (B) Computed axial tomography scan images of a representative lesion in the right hilum demonstrating continued response to treatment.
and duration of follow-up being 6.7 months. Dose reductions were required in 28.1% of patients to 37.5 mg and 9.1% of patients to 25 mg in the 4/6 schedule. Reasons for discontinuation were found to be lack of efficacy in 38.6% of patients, death in 16%, AEs in 4.3%, consent withdrawal by 4%, and others 2.7%. Response rate was 6 CRs (0.3%), 211 PRs (9%), and 1,008 SD (43.1%), with a clinical benefit rate (CR + PR + SD) of 52.3%. The median PFS was 8.9 months (95% CI: 8.3–9.9 months). The lower response rates were probably due to nonstandardized assessment in various countries. The safety profile was similar to that of the previously reposted trials.

### Unapproved Multikinase Inhibitors with Activity in Renal Cell Carcinoma

Besides sorafenib and sunitinib, there are a variety of multikinase inhibitors (MKIs) that have activity in advanced RCC patients. Various clinical trials are being conducted to

---

**Table 5.** Adverse events/toxicities seen in the phase III trial of sunitinib versus interferon-α (IFN-α)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Sunitinib (N = 375)</th>
<th>IFN-α (N = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>51 (7)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53 (5)</td>
<td>12 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>44 (3)</td>
<td>33 (1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>20 (5)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Decline in ejection fraction</td>
<td>10 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>19 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>72 (11)</td>
<td>46 (7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>71 (3)</td>
<td>64 (4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>65 (6)</td>
<td>21 (0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>60 (12)</td>
<td>63 (22)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36 (4)</td>
<td>32 (6)</td>
</tr>
<tr>
<td>Hyperamylasemia</td>
<td>32 (4)</td>
<td>28 (2)</td>
</tr>
</tbody>
</table>

elucidate, and thus define, the activity profiles of these agents. Two agents, AG-013736 (axitinib) and GW-786034 (pazopanib), appear to have significant activity.

**AG-013736**

AG-013736 (Axitinib) is an oral drug very similar to sunitinib with inhibitory effects on VEGFR-1, VEGFR-2, PDGFR, and c-KIT (23). This drug has been evaluated in the phase II setting in RCC. The available data from the phase II study have attested to its robustness against RCC (23). This trial was conducted in patients who were cytokine refractory with other standard eligibility criteria, including good performance status, measurable disease, and good organ function. The primary end point was objective response rate. Fifty-two eligible patients were started on axitinib at 5 mg bid on an empty stomach as continuous dosing. The therapy was continued until disease progression or unacceptable toxicity. RECIST evaluation demonstrated that there were 24 PRs (46%) and 21 SD (40%). The major AEs noted were hypertension, diarrhea, fatigue, nausea, and proteinuria; the majority of these AEs were ≤ grade 2. Grade 3 or 4 hypertension in eight patients (15%), diarrhea in four patients (8%), and fatigue in four patients (8%), were also reported (Table 6). Six patients had to stop the therapy due to AEs. The robust activity of this agent is a promise for RCC patients.

Rini et al. conducted a multicenter, open label, phase II study to assess the efficacy of axitinib in RCC patients who were refractory to sorafenib (24). Performance status of

| Table 6. | Adverse events in the phase II trial of axitinib in the cytokine-refractory setting |
|----------|---------------------------------|-------------------|
| **Adverse event** | **Total N (%)** | **% Grade 3 or 4** |
| Diarrhea | 24 (46) | 8 |
| Hypertension | 22 (42) | 15 |
| Fatigue | 20 (38) | 8 |
| Nausea | 19 (36) | 0 |
| Proteinuria | 19 (36) | 0 |
| Hoarseness of voice | 15 (29) | 0 |
| Anorexia | 14 (27) | 2 |
| Dyspepsia | 9 (17) | 0 |
| Stomatitis | 7 (14) | 2 |
| Vomiting | 7 (14) | 0 |

≤1, measurable disease, treated central nervous system metastases (if present), and adequate organ function were the eligibility criteria. Patients were enrolled and started on axitinib, 5 mg bid, with dose titration as tolerated. Sixty-two patients were evaluable, with a median age of 60 years and 98% having had prior nephrectomy. There were 13 PRs (21%), 21 SD (33.9%), 16 PD (25.8%), and 12 (19.3%) patients were indeterminate. Preliminary median PFS was assessed to be 7.4 months (95% CI: 5.9–9.1 months).

The activity of axitinib in the sorafenib refractory setting of metastatic RCC is promising. This suggests that there is no cross resistance between these two TKIs used in RCC.

GW-786034

GW-786034 (Pazopanib) is similar to axitinib, with activity against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-KIT. This drug is being evaluated in RCC and various other diseases currently. One phase I study showed tumor shrinkage in six out of seven RCC patients, and so phase II studies were initiated (25). The commonly seen off-target side effects of pazopanib are hypertension, diarrhea, nausea, fatigue, anorexia, vomiting, and hair depigmentation.

In the phase II trial of pazopanib, cytokine-naïve and β-refractory patients (limit of one cytokine or bevacizumab-based regimen) were enrolled if they had ECOG ≤1, measurable disease, and adequate organ function (26). Pazopanib was administered at a dose of 800 mg PO daily. RECIST assessment was done at the end of 12 weeks, and patients with response were continued on GW-786034. Patients with SD were randomly assigned to placebo or to continue pazopanib. The commonly seen toxicities were diarrhea, hair color changes, hypertension, nausea, and fatigue (Table 7). The efficacy analysis showed that out of the 225 patients, there were 69 PRs (31%), 98 SD (44%), and 37 PD (16%). Data were unknown or missing in the rest (9%). It was also found that the response rate was slightly higher (30%) in the group with prior systemic therapy than the group that was treatment naïve (26%). Most commonly seen laboratory toxicities were cytopenias, abnormal liver function tests, electrolyte imbalance, high thyroid stimulating hormone, and high amylase and lipase. Dose reduction was required for various reasons in 59 patients (26%) and dose interruptions in 45 (20%). The study is ongoing, and final analysis is pending at present.

Commonly Encountered Adverse Events with Sunitinib and Sorafenib and Their Management

The AEs and toxicity produced by sunitinib or sorafenib in the various phase II and phase III trials are summarized in Tables 3 and 5. As outlined in Table 3, the toxicity profiles of sunitinib and sorafenib are somewhat different. The most common grade 3
toxicities reported with sunitinib in the phase III trial were fatigue, diarrhea, nausea, hypertension, pancytopenia, and electrolyte abnormalities. In addition, 10% of patients had transient decrease in left ventricular ejection fraction. In this trial, 8% of patients stopped therapy due to AEs. In the TARGETs trial, the most common side effects attributed to sorafenib were rash, diarrhea, hand–foot syndrome, fatigue, alopecia, and pruritus. The most common grade 3 toxicities related to sorafenib were fatigue, hypertension, hand–foot syndrome, and hypophosphatemia. In the TARGETs trial, 21% of patients required dose reduction secondary to AEs, and treatment was discontinued in 10%. Because patient populations treated in phase III trials are quite different, direct comparison of toxicities is problematic; nevertheless, clear differences emerge such as the hematologic toxicity seen with sunitinib. The hematologic toxicity may be due to FLT-3/c-KIT inhibition in normal hematopoietic stem cells (27,28). The hair changes with sunitinib include color changes, perhaps as a result of KIT/PDGFR signal blockade, whereas with sorafenib, alopecia is more prominent (29). The skin and hair changes may be secondary to KIT/PDGFR signal blockade (29). The “off target” toxicities of these agents are also different, with hypothyroidism (30) and decreases in left ventricular systolic function reported for sunitinib, and gastrointestinal toxicity, in the form of diarrhea, reported for both. The overall AE profiles and toxicity produced by both agents are acceptable and provide therapy with an improved toxicity profile when compared to the cytokines.

Table 7. Commonly observed adverse events seen in the phase II clinical trial of pazopanib

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>All grade N (%)</th>
<th>Grade 3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>125 (56)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Hair color changes</td>
<td>89 (40)</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84 (37)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>80 (36)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>73 (32)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>49 (22)</td>
<td>—</td>
</tr>
<tr>
<td>Anorexia</td>
<td>34 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (13)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Rash</td>
<td>26 (12)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>23 (10)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22 (10)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

Managing the toxicity associated with multi-targeted kinase inhibitor administration is an important aspect of patient care when using these agents. Excessive toxicity may decrease tolerability and patient compliance.

Fatigue

Treatment-related fatigue is managed by dose modifications or breaks in therapy as needed. Use of dietary supplements or use of agents such as megestrol acetate (Megace) may not decrease this finding. In sunitinib-treated patients in one report, hypothyroidism occurred in approximately 85% of patients, of which 84% had symptoms and signs of hypothyroidism (31).

Hypertension

Hypertension is managed with commonly used antihypertensives, including thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers (Table 8). The underlying mechanism is unclear, but management considerations include various factors such as renal function, electrolyte status, and other comorbidities (e.g., coronary artery disease, diabetes). All patients should have a blood pressure (BP) cuff at home, and they should chart the fluctuation in BP on a regular basis so that the physician has a better idea of the average systolic and diastolic BP. Therapy can be complemented by the use of nonpharmacologic strategies, including dietary restrictions such as reduced salt intake, exercise, and weight control. With sunitinib, BP may decrease during therapy breaks, and close follow-up may be required.

Diarrhea

Similar to the management of treatment-related hypertension, the use of pharmacologic and nonpharmacologic modalities is emphasized in the management of diarrhea also. Clinical experience demonstrates that dietary adjustments, such as adding fruits and vegetables, fiber supplements, and rice, has been found to reduce the intensity of diarrhea (Benefiber, Metamucil, psyllium, etc.). Loperamide and diphenoxylate/atropine (Lomotil) are mainstays of drug therapy. There are clinical trials using agents such as octreotide to manage TKI-induced diarrhea. Other modalities for gastrointestinal complaints
Multi-Targeted Kinase Inhibitors in RCC

Table 8. Commonly used antihypertensives in patients treated with multikinase inhibitors

<table>
<thead>
<tr>
<th>Class</th>
<th>Representative agents that are used frequently</th>
<th>Tips for choosing agent (not recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td>Hydrochlorothiazide</td>
<td>Not a good choice for patients with severe diarrhea and electrolyte imbalance</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td></td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Atenolol</td>
<td>May be used for patients with renal function abnormalities</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Ramipril</td>
<td>Careful in using with renal function abnormalities</td>
</tr>
<tr>
<td></td>
<td>Benazepril</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosinopril</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
<td></td>
</tr>
<tr>
<td>Angiotensin receptor</td>
<td>Candesartan</td>
<td>Similar to ACE inhibitors</td>
</tr>
<tr>
<td>blockers</td>
<td>Irbesartan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olmesartan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem</td>
<td>Could be safely used in patients with diarrhea with electrolyte imbalances</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme.

*The agent could be chosen according to the need of an individual patient and the unique setting.

include the use of antacids, proton pump inhibitors, and also lactobacillus acidophilus products.

Mucositis

Mouth pain, mucosal sensitivity, and dysphagia are the usual oral symptoms. The absence of mucosal erosions could be seen in a very symptomatic patient on some occasions. Patients become accustomed to some peculiar taste patterns after taking the drug for a few weeks. Dose modification/interruptions could be tried if pain management is futile.
Hand–Foot Syndrome (Palmo-Plantar Erythrodysesthesia)

Hand–foot syndrome is a cluster of symptoms, which may include pain, blistering, pruritus, and desquamation, and callus formation on the palms and soles may be a major problem associated with sorafenib. The severity varies from patient to patient, and management includes conservative strategies. The mainstay of the treatment of this symptom includes various skin care products such as Cetaphil, Udderly Smooth, Aveeno, Norwegian formula, Bag Balm, Eucerin, Aquaphor, and Kerasal. Xerosis is managed by using moisturizing agents. Pruritus management includes various lotions and shampoos.

All of the above possible toxicities underscore the importance of a clinical nurse who is an expert in managing these symptoms.

Indications for Various Multi-Targeted Kinase Inhibitors

The data are expanding regarding the use of TKIs in RCC. But the two approved TKIs, sorafenib and sunitinib, may be used in various settings. Sunitinib has robust activity in the front-line setting and should be considered as a first-line standard of care in advanced RCC. Sorafenib prolongs refractory disease and cytokine failures, and is used as a second-line therapy. The utility of both of the agents is being investigated in the adjuvant setting, as well as the neoadjuvant setting of resectable and unresectable RCC.

Summary

Use of the newer medications is a promising strategy for managing metastatic RCC. At the same time, the dose-limiting AEs, which are the off-target effects of these agents, are a formidable challenge to manage. Well-managed toxicities promise effective long-term delivery and thus potentially longer PFS in patients who had limited hope in the not too distant past.

References

Targeting the vascular endothelial growth factor (VEGF) pathway has become the principal therapeutic strategy in the management of metastatic renal cell carcinoma (mRCC). Since their regulatory approval, sunitinib and sorafenib have been used as the standard of care in untreated mRCC patients. Despite their overall clinical activity, no durable and long-term complete responses (CRs) have been identified. Similarly, their impact on overall survival (OS) remains unknown.

Inhibition of the VEGF pathway by ligand-binding antibodies, such as bevacizumab (Avastin), has also been extensively explored and soon will become part of the daily armamentarium in the management of this epithelial malignancy.

More recently, the identification of alternative pathways, independent of VEGF and also capable of leading to tumor growth and proliferation, has resulted in U.S. Food and Drug Administration (FDA) approval of a novel mammalian target of rapamycin (mTOR) inhibitor. Similarly, other novel agents targeting specific pathways responsible for tumor progression, as well as extracellular matrix (ECM) proteins involved in angiogenesis, proliferation, and metastasis, have been reported.

In this chapter, the existing clinical data of other novel agents, different from the small tyrosine kinase inhibitors (TKIs), is reviewed that have undergone testing or that have demonstrated antitumor activity and meaningful clinical benefits in patients with mRCC.

**Rationale for Anti-Vascular Endothelial Growth Factor Antibodies in Renal Cell Carcinoma**

A better understanding of the molecular biology of RCC has led to the development of novel agents capable of inhibiting VEGF and its receptors. VEGF is a dimeric gly-
coprotein and a member of the platelet-derived growth factor superfamily of growth factors that includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor. VEGF is crucial for both normal and tumor-associated angiogenesis. The proangiogenic effects of VEGF have been well characterized and include induction of endothelial cell division and migration (1,2), promotion of endothelial cell survival through protection from apoptosis (3), and reversal of endothelial cell senescence (4). VEGF exerts its biologic effect through interaction with receptors present on the cell surface. These transmembrane tyrosine kinase receptors include VEGF receptor-1 (VEGFR-1; Flt-1) and VEGFR-2 (KDR/Flk-1), selectively expressed on vascular endothelial cells, VEGFR-3 (Flt-4), expressed on lymphatic and vascular endothelium; and the neuropilin receptor, expressed on vascular endothelium and neurons (5).

The vast majority of patients with clear cell RCC have overexpression of VEGF in tumor tissues. This overexpression is thought to be the result of the inactivation of the von Hippel-Lindau (VHL) tumor-suppressor gene that occurs in 60% of patients and has been extensively reviewed elsewhere (6).

**Bevacizumab**

Bevacizumab is a recombinant human monoclonal antibody against VEGF (bevacizumab [Avastin®], Genentech, South San Francisco, CA) that binds and neutralizes all biologically active isoforms of VEGF (6–8) (Figure 1).

The clinical activity of bevacizumab in mRCC was investigated in a randomized phase II trial in which 116 patients with cytokine-refractory metastatic clear cell RCC were randomized to receive placebo, low-dose (3 mg/kg) bevacizumab, or high-dose (HD; 10 mg/kg) bevacizumab given intravenously (IV) every 2 weeks (9). All patients had prior disease progression (PD) despite at least one systemic treatment regimen. Groups were balanced using established prognostic factors (10). The study was designed to detect a two-fold time to PD (TTPD) increase with either dose of bevacizumab versus placebo (4.8 vs. 2.5 months; *P* <.001 by log rank test). There were four RECIST (Response Evaluation Criteria in Solid Tumors)-defined partial responses (PRs) (11), all in the HD bevacizumab arm (4 of 39; 10% objective response rate [ORR]). There were no life-threatening toxicities or deaths attributable to bevacizumab. Common toxicity included hypertension and proteinuria, which were more commonly seen in the HD bevacizumab arm. All toxicities were reversible with cessation of therapy. Grade 1 or 2 hemoptysis was observed in two patients receiving bevacizumab and two patients receiving placebo. No thromboembolic events were reported in any arm.

These results were the proof-of-concept that blocking the VEGF signaling pathway is a therapeutic strategy in patients with RCC and served as the platform to rationally study other agents in combination with bevacizumab.
Considering that epidermal growth factor receptor (EGFR) also is overexpressed in RCC, a multicenter, phase II study evaluated the addition of erlotinib (Tarceva), an EGFR inhibitor, to bevacizumab in mRCC patients (12). Treatment consisted of bevacizumab, 10 mg/kg IV every 2 weeks, and erlotinib, 150 mg orally (PO) each day. Sixty-three patients were enrolled. All patients had had a nephrectomy, and 68% had received no previous systemic therapy. Fifteen patients (25%) had objective responses, and an additional 36 patients...
(61%) had stable disease (SD) after 8 weeks of treatment. Treatment was generally well tolerated; only two patients discontinued treatment because of toxicity (skin rash). Grade 1–2 skin rash and diarrhea were the most frequent treatment-related toxicities.

The additive or synergistic potential of this regimen was further evaluated in a randomized phase II trial of bevacizumab plus placebo versus bevacizumab plus erlotinib (13). This trial has been reported in an abstract form, and it demonstrated very similar response rates and progression-free survival (PFS) rates for the two arms (ORR, 13.7% vs. 14%, respectively; and PFS of 8.5 vs. 9.9 months, respectively; \( P = .58 \)). Although at the time of presentation the median OS for the bevacizumab plus placebo–treated arm had not been reached, the median OS for patients treated with the erlotinib combination was 20 months \( ( P = .16 ) \). Thus, it is not apparent from this trial that adding an EGFR-targeting agent increases the clinical activity of VEGF-targeting approaches. Additional combination trials targeting both VEGF and EGFR are under way and will further define the role, if any, of targeting EGFR in RCC.

Other Combinations with Bevacizumab

The addition of an antiangiogenic agent to standard cytokines has also been explored. Two randomized phase III trials (Europe and United States) have evaluated bevacizumab plus interferon (IFN) versus IFN alone in untreated advanced RCC patients (14). Both trials have completed accrual, and the results of the European study were recently reported (15). In this study, 649 untreated mRCC patients were randomized to receive IFN-\( \alpha \)2a plus placebo or IFN and bevacizumab. RCC histology was required to have \( >50\% \) of clear cell component. All patients had prior nephrectomy, and the performance status was \( >70\% \). Patients were also stratified by country of enrollment and by known prognostic factors (11). All patients received IFN at 9 MU (million units) subcutaneously (SC) tiw for a maximum of 52 weeks, with dose reductions allowed. Bevacizumab/placebo was administered at 10 mg/kg IV every 2 weeks until PD or drug intolerance. The primary objective of the study was to evaluate the efficacy of the combination of bevacizumab plus IFN as compared with IFN alone based on OS. Secondary objectives included PFS, TTPD, time to treatment failure, and ORR of bevacizumab plus IFN compared with IFN alone. Similarly, the safety profile of bevacizumab plus IFN, versus IFN alone, and pharmacokinetics and pharmacodynamics of bevacizumab were analyzed. By investigator assessment, the ORR observed was 31% versus 13% in favor of IFN plus bevacizumab \( ( P <.0001 ) \). The vast majority of patients achieved RECIST-defined PRs, with only three reporting CRs (one patient taking bevacizumab plus IFN and two patients in the IFN plus placebo arm). The median PFS also favored the bevacizumab plus IFN-treated arm (10.2 vs. 5.4 months, respectively; hazard ratio \( [HR] = 0.63; P <.0001 \)). Subsequent subset analyses demonstrated the good- and intermediate-risk patients appeared to benefit the most, with median PFS of 12.9 versus 7.6 months \( (HR = 0.60; P = .004) \) for the good-risk group and 10.2 versus 4.5 months \( (HR = .}
= 0.55; \( P < .0001 \)) for the intermediate-risk group. No difference in PFS was seen in the poor-risk patients receiving either combination arm. After 251 of the 450 scheduled events, the interim OS analysis suggested a survival trend in favor of the bevacizumab plus IFN combination (19.8 months for IFN plus placebo vs. no response for those receiving bevacizumab; \( P = .067 \)).

While on trial, the treatments were well tolerated, and no new toxicities emerged outside of those previously known for IFN and bevacizumab. IFN-related toxicities included fatigue and malaise observed in 15%–25% of patients in both arms. Hypertension and proteinuria was observed in 6.5% of patients receiving IFN and bevacizumab compared with 4% in IFN-treated patients. Similarly, hemorrhage, small bowel perforation, and venous/arterial thrombosis occurred in less than 3% of patients receiving bevacizumab.

Although preliminary, the lack of OS benefit found in this trial may resemble what has been observed in other randomized studies using the oral TKIs. This could certainly be due in part to the current availability and indiscriminate use of these agents for patients who have progressed after one or two prior systemic therapies. Final results from the U.S. study (Cancer and Leukemia Group B 90206) will confirm the ORR and median PFS observed in the European trial and will solidify the existing data supporting the use of bevacizumab in advanced RCC.

Other horizontal and vertical combinations using bevacizumab are currently under way. Preliminary data evaluating the efficacy and safety of bevacizumab administered in combination with either HD interleukin-2 (IL-2) (16) or low-dose IL-2 (17) have been reported in abstract form. The ORR observed in both phase II studies was approximately 13%, with no new concerning safety signals while on trial. However, in the HD IL-2 trial, there was one treatment-related death from unresponsive hypotension, which occurred during the second cycle. In both studies, typical IL-2 toxicities have been noted thus far. Similarly, hypertension and proteinuria remain the most common side effects observed with bevacizumab. Albeit preliminary, contrary to what was observed in the European randomized phase III trial of IFN plus bevacizumab versus IFN plus placebo, these results do not support the use of IL-2 (regardless of dose) when given in combination with bevacizumab.

Other bevacizumab combinations that have already demonstrated some activity in mRCC include sorafenib (Nexavar) plus bevacizumab, sunitinib (Sutent) plus bevacizumab, and temsirolimus (Torisel) and bevacizumab, among others. However, the phase I/II study evaluating the combination of bevacizumab and sorafenib has already shown some safety signals of concern. The maximum tolerated dose (MTD) in this small trial was 200 mg PO daily of sorafenib and 5 mg/kg every 2 weeks of bevacizumab (18). In contrast, the phase I study evaluating the MTD and safety of sunitinib and bevacizumab revealed that the addition of bevacizumab did not augment the known toxicities of sunitinib. Each agent was escalated to full dose, and no dose-limiting toxicities (DLTs) were observed. With regard to efficacy, the ORR observed was approximately 31% (3 of 14 patients) with an additional 50% plus of patients achieving RECIST-defined SD (19).
Another rationally designed combination reported by Merchan et al. (20) was the phase I/II study of bevacizumab plus temsirolimus. A total of 12 mRCC patients were enrolled in the phase I portion of the study. One patient in dose level 1 experienced a DLT (grade 3 hypertriglyceridemia). Another patient in dose level 2 experienced a DLT (grade 3 mucositis). Other grade 3 toxicities that were not DLTs included hypertension, proteinuria, hemorrhage, nausea/vomiting, dehydration, anorexia, pneumonitis, anemia, and hypophosphatemia. Although seven patients achieved a PR, three others had SD as best response to therapy. This study now serves as the rationale for a large randomized phase III trial evaluating IFN plus bevacizumab versus bevacizumab and temsirolimus in untreated mRCC patients.

These studies will further define the role of bevacizumab as front-line therapy in patients with advanced RCC.

**Mammalian Target of Rapamycin Inhibitors: Clinical Rationale**

Recent advances in cancer research have drawn increased interest in the use of mTOR inhibitors to treat a variety of cancers, consistent with the key roles of mTOR in cell survival, growth, protein synthesis, cellular metabolism, and angiogenesis. mTOR, which is believed to be constitutively activated in RCC by deregulated activation of the PH-domain serine/threonine oncogenes, Akt and PDK-1, or loss of the tumor suppressors phosphatase and tensin homolog (PTEN) and TSC1/TSC2, plays a role in the regulation of protein translation (21). Through the activation of the eukaryotic translation initiation factor 4E (eIF4E), which has been implicated in tumor development, and of S6 kinase, mTOR promotes the translation of messenger RNA (mRNA). In RCC, activation of mTOR by mutations that disrupt the tuberous sclerosis complex 1 and 2 genes (TSC1 and TSC2, respectively) confers a predisposition to RCC and is associated with increased hypoxia-inducible transcription factor (HIF) activity (22,23) (Figure 2). In early in vitro studies, inhibitors of mTOR down-regulate HIF activity primarily when the mTOR pathway is abnormally activated (23,24). To date, it is unclear whether HIF mediates the tumorigenic effects of mTOR; however, previous observations suggest that mTOR inhibitors may be most effective against renal cell cancers in which the mTOR pathway is abnormally activated, such as those in which the tumor suppressor PTEN, a proximal negative regulator of mTOR, is inactivated.

**Everolimus**

Everolimus (RAD001®, Novartis Pharmaceuticals, Basel, Switzerland) is an oral serine-threonine kinase derivative of rapamycin capable of inhibiting mTOR. In preclinical
models, the administration of everolimus is associated with reduction of mTOR downstream phosphorylated (p)-S6 (p-S6) and p-4E-BP1, and occasionally with increase in upstream p-Akt. Several phase I and II studies evaluating dose, schedule, and the pharmacodynamics of everolimus have been reported and are discussed elsewhere (25–29).
Amato and colleagues (30) conducted a phase II trial in which 41 previously treated mRCC patients received oral RAD001 at a dose of 10 mg daily without an interruption (28-day cycle), with dose modifications for toxicity. The ORR observed was 33% (12 of 37), and 19 patients had SD of 3+ months, with a median duration of therapy of 8 months (range, 1+ to 20+). Treatment-related adverse events included mucositis, skin rash, pneumonitis, hypophosphatemia, hyperglycemia, thrombocytopenia, anemia, and elevated liver function tests.

Currently, a large phase III trial evaluating everolimus plus best supportive care (BSC) versus placebo plus BSC is under way in Europe. This is an attractive trial testing the concept of sequential therapy that plans to accrue more than 300 patients with TKI-refractory mRCC, a common theme now seen in the mRCC population.

**Temsirolimus**

Temsirolimus (CCI-779®, Wyeth Pharmaceuticals, Madison, NJ), is another inhibitor of mTOR, a molecule implicated in multiple tumor-promoting intracellular signaling pathways, including HIF transcription (31,32). Preliminary phase I data led to the design of a phase II trial in patients with treatment-refractory mRCC. In this study, 111 patients were randomized to one of multiple dose levels (25 mg, 75 mg, or 250 mg IV weekly) (33). The overall response rate was 7%, with additional patients demonstrating minor responses. Given the high number of dose reductions and treatment discontinuations at the higher dose levels, the investigators advocated the 25 mg IV weekly dose for future temsirolimus studies. Retrospective assignment of risk criteria to patients in this study identified a poor-prognosis group (N = 49). Temsirolimus-treated patients in this poor-prognosis group had a median OS of 8.2 months compared to 4.9 months for first-line IFN-treated patients (historical controls, N = 437). Loss of PTEN may be more common in poor-risk patients and may account for this finding, as mutation of this tumor suppressor gene would activate mTOR and potentially increase the relevance of mTOR-targeted therapy in this subgroup (34). A subsequent randomized phase III trial was conducted in patients with poor-risk mRCC as defined by existing prognostic schema (35). Patients with mRCC and no prior systemic therapy were enrolled in this open-label study if they had three or more of six adverse risk factors (Karnofsky performance status <80%, time to metastatic disease <1 year, hemoglobin < lower limit of normal, lactic acid dehydrogenase >1.5x upper limit of normal, corrected serum calcium >10 mg/dL, and >1 metastatic disease site) (10,36). Patients were equally randomized to receive IFN up to 18 MU SC tiw; temsirolimus, 25 mg IV once per week; or temsirolimus, 15 mg IV once per week plus IFN 6 MU SC tiw. The primary study end point was OS, and the study was powered to compare each of the temsirolimus-containing arms to the IFN arm. Preliminary results demonstrated that patients treated with temsirolimus had a statistically longer survival than those treated with IFN alone (10.9 months vs. 7.3 months; \( P = .0069 \)). OS of patients treated with IFN and temsirolimus plus IFN were not statisti-
Novel Strategies in the Management of Advanced Renal Cell Carcinoma

Immunomodulatory Agents

Thalidomide

Thalidomide (Thalomid®, Celgene Corporation, Summit, NJ) is a drug with immunomodulatory as well as antiangiogenic properties. It reduces the expression of potent angiogenic factors such as basic fibroblast growth factor (bFGF), VEGF, and tumor necrosis factor (TNF) (38,39). It suppresses TNF production by enhancing the degradation of TNF mRNA in monocytes (40,41). The clinical activity of thalidomide in mRCC has been extensively studied. Several phase II trials using different doses and schedules that have ranged from 100 mg/day to 1,200 mg/day have shown that more than 30% of patients experience SD while on treatment, with only a modest objective response in the range of 4%–17% (42–50).

To investigate whether escalating doses of thalidomide would lead to more activity in mRCC, Lee et al. (51) conducted a randomized phase II trial in which 60 patients with cytokine-refractory mRCC were randomized to receive either thalidomide starting at
100 mg/day PO and escalated by 100 mg/day every 2 weeks to the maximum dose of 400 mg/day or medroxyprogesterone (MPG) at a fixed dose of 300 mg PO daily. Of the 48 evaluable patients (22 thalidomide and 26 MPG), no responses were observed. Three patients (10.3%) experienced SD, which lasted 5+ (175 days), 6+ (182 days), and 12 months (364 days), respectively. The median duration of treatment was no different from the MPG arm, 73 days (range, 14 to 364 days) versus 84 days (range, 7 to 175 days), respectively. Median survival of patients treated with thalidomide (N = 29) was 8.2 months (245 days) compared with 4.8 months (144 days) in the MPG arm (P = .62).

The most common toxicities were somnolence, constipation, fatigue, and paresthesias. Less common toxicities included rash and nausea. Of the 26 assessable patients, three patients came off study after less than 3 weeks because of grade 2 somnolence and grade 3 fatigue at 200 mg/day (N = 1), grade 3 arrhythmia (supraventricular tachycardia) at 100 mg/day (N = 1), and pulmonary embolus at 200 mg/day (N = 1). The other 23 patients had at least 4 weeks’ treatment. Constipation was generally manageable using standard supportive measures, whereas somnolence and fatigue mostly improved on dose interruption or cessation. Two patients in the thalidomide arm developed thromboembolic events. The only hematologic toxicity was grade 1 neutropenia (N = 4). None of these was of clinical consequence, and all resolved completely either while still on treatment (N = 3) or on cessation of treatment (N = 1).

In summary, all of the studies discussed demonstrate that thalidomide has a very modest activity in mRCC and that the risk/benefit ratio clearly does not favor the use of thalidomide in the vast majority of patients with mRCC.

**Lenalidomide**

Lenalidomide (Revlimid®, Celgene Corporation, Summit, NJ) is a structural analog of thalidomide that has more potency and fewer non-hematologic side effects (52). It has been demonstrated that lenalidomide has antiangiogenic activity through the inhibition of bFGF-induced, VEGF-induced, and TNF-α-induced endothelial cell migration, which is caused at least in part by the inhibition of the Akt phosphorylation response to bFGF (53). In addition, lenalidomide stimulates T-cell proliferation and the production of IL-2, IL-10, and IFN-γ, inhibits IL-1β and IL-6; and modulates IL-12 production (22). T-cell–derived IL-2 production is achieved at least in part through up-regulation of the transcriptional factor API1 activity (54,55).

Two different phase II two-stage design trials tested the activity of this immunomodulatory agent in patients with advanced RCC. In the first study, Marsh’s group (56) enrolled 41 cytokine-refractory mRCC patients. Patients received lenalidomide at 25 mg PO on days 1–21 (28-day cycle). Forty-one percent of patients had not received prior systemic therapy. Similarly, the vast majority of patients (85%) had clear-cell histology. Most of the patients were either good- or intermediate-risk patients (31% good risk and 59% intermediate). Among all evaluable patients (N = 39), only one patient achieved a
RECIST-defined CR, and two (5%) had confirmed PRs. The vast majority of patients (54%) had SD lasting >12 weeks. The median time to progression (TTP) reported was 5.6 months, and the median OS was 16 months (1–28+ months). Most common toxicities included grade 1–2 fatigue, diarrhea, and constipation. Grade 3 neutropenia occurred in 15 of 39 patients, with less than 5% of patients developing grade 4 thrombocytopenia or neutropenia.

The second phase II study was conducted by our group at the Cleveland Clinic Taussig Cancer Institute (58) in which 28 patients with advanced RCC received lenalidomide at 25 mg PO on days 1–21 (28-day cycle). Fifty-seven percent of the patients had received prior systemic therapy, and 100% had undergone prior nephrectomy. Similar to Marsh’s trial, the vast majority of patients had good- and intermediate-risk disease (36% and 61%, respectively). Three of 28 patients (11%) demonstrated a PR and at the time of publication continued to be progression free for >15 months. Eleven patients (39%) had SD lasting >3 months, eight of whom had tumor shrinkage. A total of six patients (21%) remain on trial, with five additional patients continuing to be followed for survival. The median follow-up for those 11 patients is 13.5 months (range, 8.3–17.0 months). Median survival has not been reached. The treatment was well tolerated by most patients. The most commonly reported adverse events were fatigue (86%, severe in 11%), neutropenia (65%, severe in 36%), and skin reactions (68%, severe in 11%). Thrombocytopenia occurred in 57% of patients, with 11% having grade 3 toxicity; no patient developed bleeding or required platelet transfusions.

Although the true mechanism of action responsible for the modest activity of this agent in mRCC remains unknown, there appears to be a small subset of patients who may benefit from this type of immunomodulatory activity. With the current explosion of other novel compounds, some of which have already shown solid clinical activity against RCC, it is unlikely that lenalidomide will be further developed in RCC.

Atrasentan and the Rationale for Endothelin Inhibition in Advanced Renal Cell Carcinoma

The endothelins (ETs) are a family of three separate 21-amino-acid peptides (ET-1, ET-2, and ET-3) produced by endothelial cells and originally described as potent vasoconstrictors (58,59). Recent studies demonstrate that ETs are also involved in cell proliferation, cell migration, apoptosis, and angiogenesis (60). ET-1 has been implicated in several of the molecular pathways that lead to tumor proliferation. These include angiogenesis, tumor invasion, tumor cell proliferation, and apoptosis (61–66). ET-1 has demonstrated the ability to induce neovascularization via ET-receptor stimulation. Overexpression of ET-1 and its receptor is directly correlated with increased microvessel density and VEGF overexpression. Activation of ET-A also facilitates the migration of vascular smooth muscle cells and pericytes—an important step in neovascularization. Furthermore, ET-1 stimulates VEGF secretion in a dose-dependent fashion, facilitating endothelial cell
proliferation. As it is the case with clear renal cell carcinoma, atrasentan is an orally bioavailable ET inhibitor that selectively binds and blocks the effects of ET-1. As such it is perhaps the most active ET antagonist in cancer therapeutics. Atrasentan has already demonstrated activity in patients with RCC included in phase I studies (67,68). Based on these preliminary findings, a phase II Eastern Cooperative Oncology Group (ECOG) study was undertaken in patients with measurable or nonmeasurable (bone only) mRCC (69). Patients received atrasentan, 10 mg/day PO, until PD or unacceptable toxicity. The primary end point was a progression-free rate at 6 months. Median duration of treatment was 10 weeks (range, 2–107 weeks). Toxicities were mild, with 73% of patients reporting no grade 3 or higher treatment-related adverse events. Grade 4 adverse events included neutropenia (N = 3), dyspnea (N = 2), thrombosis, and supraventricular arrhythmia (N = 1 each). Median PFS was 2.3 months (95% confidence interval [CI], 2.0–3.5 months). Although atrasentan was well tolerated, these results demonstrated the lack of activity of this novel agent; thus further testing of this compound is not warranted.

**Nuclear Factor κB Inhibitors in Advanced Renal Cell Carcinoma**

Other dysregulated proteins that are targeted for degradation and are potentially important in RCC include p53; p27; cyclins D1, E, and B; major histocompatibility complex-1–restricted IκB, an inhibitor of nuclear factor κB (NF-κB); and transcription factors of the AP-1 family (69). Among these molecules, activation of NF-κB by proteolysis represents one of the most critical steps shown to be related to tumor growth. Although initially considered a mediator of immune and inflammatory responses by its ability to induce expression of genes encoding cytokines, cytokine receptors, and cell-adhesion molecules, recent data suggest that NF-κB plays a role in cellular growth, angiogenesis, and migration (70,71). Induction of functional defects in host T lymphocytes by tumor is thought to be critical in immune evasion by solid malignancies, especially RCC (72). Increased activation of NF-κB may be responsible for the clonal selection of RCC through the production of inflammatory cytokines, which provide autocrine growth and selective survival. Additionally, in vitro inhibition of the constitutive activation of NF-κB in RCC leads to the induction of apoptosis (38,39).

To date, several reversible and irreversible 20S/26S inhibitors have been developed (73). Among those, bortezomib (Velcade®, Millennium Pharmaceuticals Inc., Cambridge, MA; formerly PS-341), a boronic acid dipeptide, acts as a unique reversible inhibitor of the proteasome pathway by inhibiting the chymotryptic activity of the proteasome, resulting in the attenuation of the degradation of cell cycle regulatory proteins (74). Based on the preclinical work demonstrating the importance of the proteasome/NF-κB pathway in RCC, two phase II trials evaluating the activity of bortezomib in advanced cytokine-refractory RCC patients were conducted. In the trial by the University of Chicago group (75), 21 patients with advanced RCC received 1.5 mg/m² of bortezomib administered IV...
twice weekly for 2 weeks every 21 days. In the absence of grade 3–4 toxicities, dose escalation to 1.7 mg/m² was allowed. The primary end points of this study were response and safety. Patients were evaluated weekly for toxicity, and disease response assessment was performed every three cycles using RECIST criteria. To assess proteasome inhibition, investigators also randomly assigned patients to tumor core biopsies either before the first dose or after the third cycle of bortezomib. Only 21 of 23 enrolled patients received therapy. The overall response rate was 5% (95% CI, 0.05%–9.5%), with one PR. An additional six patients (28%) had SD for a median of 12 weeks (range, 9–18 weeks). Among all patients, 86% completed three or more cycles of therapy, whereas 14% experienced clinical PD before three cycles. The study was discontinued in the first stage after observing a single response. With regards to the correlative studies proposed, inadequate timing and insufficient sample numbers preclude conclusions regarding whether the dose and schedule were sufficient to cause proteasome inhibition within the tumor tissue. With a similar design, Kondagunta and colleagues (76) evaluated 37 patients with advanced RCC. Similar to the Chicago experience, almost one-half of the patients had received no systemic treatment for their disease. Patients received 1.5 mg/m² of bortezomib twice weekly for 2 consecutive weeks followed by a 1-week rest period. The last 12 patients on trial received a lower dose of bortezomib (1.3 mg/m²) due to the fact that more than 50% of patients enrolled in the first stage of the study required dose reductions secondary to toxicities. Of the 37 patients assessable for response, four (11%; 95% CI, 3%–25%) achieved a RECIST-defined PR, whereas 14 (38%; 95% CI, 23%–55%) had SD. The median TTP was 1.4 months (95% CI; 1.2–3.4 months). The 6-month PFS rate was 24% (95% CI, 11%–38%).

Similar to what has been observed in multiple myeloma studies, the most common toxicities encountered in the two RCC phase II trials included grade 1–2 fatigue, sensory neuropathy, nausea, dyspnea, constipation, anemia, thrombocytopenia, and transaminitis. Although in the Chicago study three patients developed grade 4 toxicities (arthralgia, diarrhea, and vomiting), in the study by Kondagunta’s group, no grade 4 toxicities were observed.

Despite the biologic rationale for targeting the proteasome pathway in RCC, these two well-conducted trials have failed to demonstrate the clinical utility of this agent in this epithelial neoplasm. Although PRs were observed in both trials, when compared with other contemporary agents currently available, bortezomib’s antitumor activity in RCC is quite limited. Although this pathway remains of importance in RCC biology, further testing of proteasome inhibitors in RCC should only be pursued in the context of a clinical trial using biologic markers capable of predicting response.

**Inhibition of Extracellular Matrix Proteins**

Integrins are cell-adhesion matrix glycoproteins with key roles in biologic processes such as angiogenesis, platelet aggregation, and lymphocyte homing. Integrins bind to matrix
components and transduce extracellular stimuli into intracellular signaling effects (outside-in signaling) and vice versa (inside-out signaling) (77). Such integrin-mediated cell-matrix interactions regulate cellular effects, including cell proliferation, survival, adhesion, and migration. Integrins form heterodimers consisting of noncovalently linked $\alpha$ and $\beta$ sub-units, the combination of which determines specificity for ECM proteins. Integrins, including $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 5\beta 1$, are up-regulated during angiogenesis as determined from targeted deletions in genetic mouse models and using antagonists that inhibit in vitro and in vivo angiogenesis. They also have demonstrated important roles in endothelial cell proliferation, survival, migration, vessel maturation, and remodeling (77,78).

**Volociximab**

Volociximab (M200®, PDL Pharmaceuticals, South San Francisco, CA) is a chimeric monoclonal antibody with high, subnanomolar affinity for the $\alpha 5\beta 1$ integrin receptor of endothelial cells. Although $\alpha 5\beta 1$ is implicated in tumor angiogenesis, its precise mechanism of action is not well defined. Consequently, the in vivo mechanism of action of volociximab is yet to be elucidated. Potential mechanisms of action might include regulation of angiogenesis via modulation of proliferation and survival of endothelial cells, and during subsequent vessel organization (cell adhesion and matrix interactions), maturation, and remodeling events. It is also thought that volociximab inhibits the binding of the endothelial cells to fibronectin (79,80).

The final results of a multicenter open-label, phase II, two-stage design trial demonstrated very modest activity in advanced RCC (81). In this study, 40 patients with cytokine-refractory RCC received volociximab, 10 mg/kg IV every 2 weeks, until DP or drug intolerance. All patients were evaluated for efficacy every 8 weeks using RECIST criteria. Prior nephrectomy occurred in 38 patients (95%). Nineteen patients (47.5%) had more than two prior therapies. Twenty-one patients (52.5%) had prior antiangiogenic therapy. Other prior treatments included IL-2 in 15 patients (37.5%), IFN-$\alpha$ in seven (17.5%), and IL-2 plus IFN in two patients (5%). Most frequent side effects included fatigue in 27 patients (67.5%), nausea in 14 (35%), dyspnea in eight (20%), and arthralgias in seven (17.5%), of which none was grade 3 or 4. SD was observed in 32 patients (80%), including one confirmed PR. Duration of SD ranged from 2 to 22 months. Fourteen patients (35%) had TTP between 5.8 and 22.0 months. Four patients (10%) had TTP >14 months (range, 14–22 months), eight patients (20%) had TTP >6 months (range, 6–12 months), and two patients (5%) had TTP of 5.8 months. Median TTP was 4 months. Median OS had not been reached after 22 months. OS at 6 months was 79% and 68% at 22 months. Six patients (15%) died in the study, five patients (12.5%) due to progressive disease and one with arrhythmia (unrelated to volociximab). Other side effects observed included grade 1 and 2 fatigue, nausea, dyspnea, and headache. No grade 3 or 4 side effects were observed.

In summary, this study demonstrated that inhibition of endothelial cell-matrix interactions may be a rational therapeutic target in RCC. Although volociximab failed to
demonstrate an OR, several patients on trial have enjoyed prolonged progression-free disease for a long period. With the understanding of the relationship between pVHL, VEGF expression, and endothelial cell matrix, trials pursuing dual inhibition of VEGF and integrin signaling pathways may be of interest.

**Future of Novel Molecules in Advanced Renal Cell Carcinoma**

Better understanding of the molecular pathogenesis of RCC has resulted in the development of several novel targeted approaches with clear antitumor activity. Although comparisons across existing phase II and III trials in RCC should not be routinely done, it is clear that most patients receiving any of these therapies do experience some clinical benefit; however, the impact of this “benefit” on PFS or OS remains unknown. Further investigation of the relationship among magnitude and duration of clinical benefit (CR + PR + SD) with TTP and OS is warranted.

The recent explosion of potentially active agents in RCC leads to important questions regarding agent selection, timing of initiation, number of agents, sequencing, and their utility in refractory settings. These questions, coupled with new molecular and genetic markers that can predict an individual’s tumor behavior, need to be addressed in prospective clinical trials.

Finally, further work and more collaboration between clinicians and scientists is required to broaden the understanding of this disease and continue with the success and progress that has been observed over the past few years in the management of this challenging epithelial malignancy.

**References**

112 Novel Strategies in the Management of Advanced Renal Cell Carcinoma


Novel Strategies in the Management of Advanced Renal Cell Carcinoma

Adjuvant and Neoadjuvant Therapy for Renal Cell Carcinoma: Past and Future Strategies

David A. Kunkle, MD, and Robert G. Uzzo, MD

Cancer of the kidney accounts for approximately 3.5% of all malignancies and is the third most common cancer of the urinary tract (1). With an estimated 51,190 new cases occurring in 2007 and 12,890 deaths attributable to the disease, renal cell carcinoma (RCC) is the most lethal of all genitourinary tumors (1).

Like most malignancies, RCC is a heterogeneous disease. This heterogeneity is reflected in its presentation, pathology, molecular biology, and clinical course. Patients may exhibit a variety of symptoms at presentation, including any of the classic triad of flank pain, hematuria, and a palpable abdominal mass (2). Nonspecific symptoms at presentation may include fatigue, weight loss, or anemia (2). However, the most common presentation is an asymptomatic patient undergoing body imaging as generalized screening for unrelated symptomatology (3). Pathologic heterogeneity is illustrated by at least six distinct histologic subtypes—(a) clear cell, (b) papillary, (c) chromophobe, (d) medullary, (e) collecting duct, and (f) unclassified—which exhibit varying degrees of biologic aggressiveness (4). Similarly, considerable variability is seen with regard to tumor grade, which accounts for nuclear and nucleolar size, shape, and content (5). Emerging data from molecular analyses indicate that RCC subtypes exhibit a variety of molecular tumor markers and unique patterns of gene expression (6,7). Clinically, the disease behaves quite heterogeneously, with courses ranging from indolent to highly aggressive. Although relatively few data exist regarding the natural history of untreated RCC, recent data demonstrate that most small renal tumors exhibit slow, albeit variable, growth kinetics (8). Furthermore, approximately 30% of small renal tumors will not demonstrate interval growth at a median of 29 months of active surveillance (9).
For most cases of RCC, surgical monotherapy (or as part of a multimodal approach) remains the standard of care. In patients with early localized disease, radical nephrectomy is associated with a 5-year cancer-specific survival (CSS) as high as 97% for pT1a lesions and 87% for pT1b tumors, whereas nephron-sparing surgery is associated with 5- and 10-year CSS of 96% and 90%, respectively, for tumors ≤4 cm (10,11). Early data for patients receiving laparoscopic partial nephrectomy are similarly favorable, with 100% CSS at 5-year median follow-up (12). Additionally, minimally invasive ablative technologies are emerging as potential treatment options for clinically localized RCC with high associated short and medium CSS rates (13). Although data are not yet available to determine the long-term effectiveness of these treatment modalities, it should be emphasized that the natural history of a small, localized, incidentally detected tumor appears indolent. There appears to be a low risk of progression to metastatic disease over a median of 36 months under active surveillance, suggesting the possibility of overtreatment bias in many ablative studies (8).

However, 20% of patients at presentation have either locally advanced RCC or spread to regional lymph nodes, whereas another 22% have metastatic RCC (mRCC) (1). Figure 1 depicts 5- and 10-year survival rates for patients presenting with localized, regionally...
advanced mRCC. Unlike the outcomes in early localized disease, survival rates for node-positive (N+) patients are 11%–35% at 5 years (4), and patients with N+ mRCC are rarely cured despite aggressive multimodal therapy. Cytoreductive nephrectomy with systemic therapy in mRCC is associated with few cures and poor CSS outcomes, with median survivals of 12–24 months (14–18). Moreover, patients with metastatic disease have rates of response to biologic agents such as interferon-α (IFN-α) and/or interleukin-2 (IL-2) of only 5%–20% (19–21). Recent data pertaining to the use of tyrosine kinase inhibitors (TKIs) for patients with advanced disease have shown response rates of 10%–42% and disease stabilization in another 26%–74% of patients (22,23).

Between the extremes of early incidental RCC and mRCC exists a gradation of risk. Twenty percent to 40% of patients undergoing surgical resection for localized RCC experience recurrence (4), suggesting that there are some individuals in whom surgical excision is necessary but insufficient due to the presence of micrometastatic disease. In these patients, the development of effective adjuvant strategies is imperative. The use of adjuvant therapies to treat patients with high-risk malignancies has been explored for many different solid tumors. These efforts seek to eradicate micrometastatic populations of cells that have escaped local surgical control by using systemic therapies. There have been relatively few adjuvant studies in RCC for several reasons, including a lack of previously demonstrated effective systemic therapies for RCC in the metastatic setting, toxicity concerns, and historic difficulties recruiting to multi-institutional and cooperative group adjuvant trials for RCC.

In this chapter, we discuss the prognostic variables and comprehensive staging algorithms for identifying patients at high risk for disease recurrence after surgery for RCC. Additionally, we review important historical studies, as well as highlight ongoing clinical trials and future strategies for adjuvant and neoadjuvant treatment in this patient population.

Prognostic Variables in Renal Cell Carcinoma

Accurate methods for predicting which patients are at high risk for disease recurrence and progression allow identification and selection of those patients most likely to benefit from conventional and novel therapies. Clinical, anatomic, histologic, and molecular variables in RCC have been shown to be associated with patient outcomes after surgical resection (Table 1).

Important clinical prognostic characteristics for patients with RCC include the presence of symptoms at presentation, performance status, cachexia, and several laboratory parameters. Patients with symptoms attributable to the primary tumor on presentation appear to have a significantly worse prognosis than those with incidentally detected tumors, although this difference may be lost when controlling for stage (24). Overall health status as determined by the Karnofsky scale or Eastern Cooperative Oncology Group performance status (ECOG-PS) has been closely correlated with survival. Patients with an ECOG-PS ≥1 have a 5-year survival rate of 51% compared to the 81% 5-year
Table 1. Anatomic, histologic, and clinical predictors and potential molecular markers for renal cell carcinoma (RCC)

<table>
<thead>
<tr>
<th>Anatomic</th>
<th>Histologic</th>
<th>Clinical</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>Nuclear grade</td>
<td>Localized symptoms</td>
<td>Hypoxia inducible:</td>
</tr>
<tr>
<td>Tumor extension</td>
<td>Histologic subtype</td>
<td>Performance status</td>
<td>CA IX</td>
</tr>
<tr>
<td>Adrenal involvement</td>
<td>Presence of sarcomatoid features</td>
<td>Cachexia</td>
<td>CA XII</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>Presence of histologic necrosis</td>
<td>Thrombocytosis</td>
<td>VEGF</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>Macrosopic tumor necrosis</td>
<td>Anemia</td>
<td>Insulin-like growth factor-1</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Collecting system invasion</td>
<td>Hypercalcemia</td>
<td>CXCR4</td>
</tr>
<tr>
<td>Renal sinus fat invasion</td>
<td>Microvascular invasion</td>
<td>Elevated alkaline phosphatase</td>
<td>Hypoxia-inducible transcription factor-1α</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated C-reactive protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated erythrocyte sedimentation rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Percent body fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>American Society of Anesthesiologists score</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CXCR3 (chemokine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum erythropoietin levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proliferation:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KI-67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ag-NORs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell-cycle regulation:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PTEN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bcl-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclin A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cell adhesion:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EpCAM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E-cadherin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>α-Catenin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cadherin-6</td>
</tr>
</tbody>
</table>
Miscellaneous:
  - Gelsolin
  - Vimentin
  - VEGF receptor
  - CA-125
  - CD44
  - Androgen receptors
  - Caveolin-1
  - Transforming growth factor-β

Cytogenetics:
  - Aberrant DNA methylation
  - Loss of 3p, 9p, and trisomy 17 in papillary RCC
  - Loss or polysomy of 3p in clear cell RCC
  - von Hippel-Lindau mutation
  - Increased expression of myc target gene MINA53

CA = carbonic anhydrase; CXCR = CXC chemokine receptor; VEGF = vascular endothelial growth factor.
survival for patients with a score of 0 (25). Cachexia and thrombocytosis (platelet count $\geq 450,000$) may also predict worse survival (26,27). Additional laboratory parameters that may correlate with poor outcomes include anemia (hemoglobin $<10$ g/dL for females, $<12$ g/dL for males), hypercalcemia, elevated alkaline phosphatase, elevated C-reactive protein, and an elevated erythrocyte sedimentation rate (24).

Currently, the most commonly used pathologic staging system for RCC is the International Union against Cancer and the American Joint Committee on Cancer tumor, node, metastasis (TNM) staging system. Importantly, tumor stage remains the single best prognostic indicator. Pathologic TNM staging incorporates important anatomic prognostic variables such as tumor size; local tumor extension; adrenal, venous, and/or lymphatic involvement; and distant metastases. Modifications made in 2002 have improved the prognostic ability over the 1997 staging system and have been validated in published reports (10). These adjustments included subclassification of pT1 tumors as pT1a ($<4$ cm) and pT1b (4–7 cm), grouping extension into the renal vein and inferior vena cava (IVC) below the diaphragm as T3b, and reclassifying IVC involvement above the diaphragm as T3c. Estimated 5-year CSS by the 2002 tumor classification is 97% (pT1a), 87% (pT1b), 71% (pT2), 53% (pT3a), 44% (pT3b), 37% (pT3c), and 20% (pT4), respectively (10).

In addition to TNM stage, several other histologic characteristics have been shown to be independent prognostic indicators of disease progression and survival for RCC. Fuhrman nuclear grade, histologic subtype, and the presence of sarcomatoid features or histologic necrosis provide additional prognostic information for patients with localized RCC. Studies have indicated a significant correlation between tumor grade and survival, independent of anatomic stage (28). Patients with T1 tumors demonstrate 5-year CSS rates of 91%, 83%, 60%, and 0% for grades 1–4, respectively (29). The papillary histologic subtype of RCC has been subclassified as type I (low grade) and type II (high grade), with type II an independent predictor of poor survival (25). Patients with chromophobe RCC seem to demonstrate improved survival compared to other subtypes (4). Collecting duct carcinomas behave aggressively and have a poor prognosis (4). Histologic findings of sarcomatoid features are found in $<5\%$ of RCCs and are associated with a poor outcome (28). Five- and 10-year survival rates when sarcomatoid features, characterized by a spindle cell growth pattern, are present are 22% and 13%, respectively (30). Likewise, histologic necrosis has been associated with poor outcomes, with such patients demonstrating a two- to threefold higher likelihood of death from RCC than those without necrosis (4). Although the histologic finding of invasion into the collecting system does not affect survival in high-stage tumors (T3), it is associated with a worse prognosis for low-stage disease (31).

Using molecular analyses, a variety of molecular tumor markers have been examined as prognostic tools in RCC. Carbonic anhydrase IX (CA IX) is perhaps the most significant molecular marker for RCC to date. CA IX is a cell surface transmembrane CA located downstream of the von Hippel-Lindau (VHL) tumor-suppressor gene and upregulated by the hypoxia-inducible pathway (32). CA IX is thought to be involved in
tumor cell regulation of intracellular and extracellular pH during periods of hypoxia, thus permitting malignant cells to proliferate and metastasize (33). CA IX is not expressed by normal fetal or adult kidney specimens and serves as a strong biomarker for kidney cancer, particularly clear cell RCC (34). In a multivariate analysis controlling for tumor T stage, Fuhrman grade, nodal involvement, and performance status, patients with mRCC and <85% CA IX expression had a significantly worse disease-free survival (DFS) (35). Low CA IX expression was also associated with a worse prognosis for patients with clinically localized high-risk tumors (35).

Other biomarkers that have been linked to RCC include p53, gelsolin, Ki67, vimentin, phosphatase and tensin homolog (PTEN), Ep-CAM, and CA XII. An increase in p53, gelsolin, Ki67, and vimentin staining have all been correlated with worse prognosis, whereas decreased staining correlates with worse prognosis for PTEN, Ep-CAM, and CA XII (36). The p53 protein is involved in cell cycle regulation, and mutations have been associated with cellular proliferation and decreased apoptosis. Gelsolin functions in the splitting of actin during cell motility, and Ki67 is a nuclear antigen selectively expressed in proliferating cells with activity that may reflect biologic aggressiveness (37). Vimentin staining has been identified as an independent predictor of poor prognosis in RCC (6). On multivariate analysis, CA IX, vimentin, and p53 were shown to be statistically significant predictors of survival, independent of T stage, metastatic status, performance status, and histologic grade (4). Vascular endothelial growth factor (VEGF), a modulator of angiogenesis, has also been implicated in RCC, and high serum levels of VEGF have been associated with increased risk of recurrence in early stage disease (38).

A molecular marker that has recently been investigated in renal cancers is aberrant DNA methylation. Methylation at cytosines, located at CpG dinucleotides, is a ubiquitous but regulated phenomenon essential for normal mammalian development (39). Epigenetic hypermethylation of CpG islands in the promoter regions of genes is associated with transcriptional silencing and is a frequent event in human cancer (40). Quantitative gene methylation profiling has been used to identify unique patterns of gene methylation among distinct histologic subtypes of RCC (7,20). Silencing of tumor suppressor genes, such as p16, VHL, BRCA1, and the mismatch repair gene hMLH1, have established promoter hypermethylation as a common mechanism for tumor suppressor inactivation in human cancer and as a promising new target for molecular detection (20). Several cancer genes important in RCC, including p16 and VHL, have been found to have hypermethylation of normally unmethylated CpG islands within the promoter regions in kidney cancer cells (39–41). A profile published in 2004 describes methylation patterns in RCC of differing stages and histopathologies (41). The presence or absence of hypermethylation may prove to be a useful predictor of response to therapy or risk of relapse.
Stratification of Risk and Prognostic Nomograms

Prognostic algorithms for overall and disease-specific survival in patients with RCC have been constructed by investigators at several institutions to assist clinicians and patients in quantitating the risk of recurrence (Table 2). Accurate prediction of recurrence after surgical resection is valuable for counseling, individualizing patient follow-up, and identifying/selecting high-risk patients for adjuvant therapy protocols. Nomograms consist of graphic depictions of prediction models accounting for multiple prognostic variables simultaneously. These tools make unbiased predictions based on objective data and assist clinicians and researchers in the stratification of risk, which is useful in clinical care and research.

Memorial Sloan-Kettering Cancer Center Nomograms

The first nomogram to predict freedom from recurrence after partial or radical nephrectomy was developed in 2001 by investigators at the Memorial Sloan-Kettering Cancer Center (MSKCC). This algorithm could be used to predict prognosis for patients with localized clear cell, papillary, or chromophobe RCC (42). The model included characteristics of tumor stage, tumor size, histologic subtype, and symptoms at presentation. The MSKCC nomogram was subsequently revised in 2005, focusing on the clear cell histologic variant (43). This adjusted predictive model incorporated data regarding the TNM stage, tumor size, Fuhrman grade, presence of necrosis, microvascular invasion, and clinical presentation as prognostic factors.

Similarly, investigators at MSKCC have studied prognostic variables for previously treated patients with mRCC. Motzer et al. retrospectively reviewed 463 patients with mRCC who were treated with IFN-α for mRCC and developed a scoring algorithm to predict outcome (44). In a multivariate analysis of nine potential prognostic factors, performance status, lactate dehydrogenase level, hemoglobin level, corrected serum calcium level, and time from diagnosis to immunotherapy were found to be associated independently with survival. Notably, only 55% of patients in this study underwent nephrectomy, which was associated univariately with improved survival. A subsequent analysis examined the relationship between pretreatment clinical features, and survival was studied in 251 patients with advanced RCC treated during 29 consecutive clinical trials between 1975 and 2002 (45). Poor prognostic features found to be significant were low hemoglobin, high corrected calcium, and low performance status. The number of risk factors present was inversely correlated with survival according to these criteria.

University of California, Los Angeles Nomograms

The University of California, Los Angeles Integrated Staging System (UISS) was initially based on 661 patients with RCC and was designed to provide a simple and accurate
### Table 2. Prognostic staging systems for stratification of risk

<table>
<thead>
<tr>
<th>Institution/staging system</th>
<th>Year</th>
<th>Extent of disease</th>
<th>Tumor subtype</th>
<th>Prognostic indicators</th>
<th>Prognostic information</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC (42)</td>
<td>2001</td>
<td>Localized</td>
<td>All</td>
<td>TNM stage, tumor size, histology, symptoms</td>
<td>Recurrence</td>
<td>Nomogram</td>
</tr>
<tr>
<td>MSKCC (45)</td>
<td>2004</td>
<td>Metastatic</td>
<td>All</td>
<td>Anemia, corrected calcium level, performance status</td>
<td>Survival</td>
<td>Algorithm</td>
</tr>
<tr>
<td>MSKCC (43)</td>
<td>2005</td>
<td>Localized</td>
<td>Clear cell</td>
<td>TNM stage, tumor size, nuclear grade, histologic necrosis, microvascular invasion, symptoms</td>
<td>Recurrence</td>
<td>Nomogram</td>
</tr>
<tr>
<td>UCLA (UISS) (46)</td>
<td>2001</td>
<td>Localized</td>
<td>All</td>
<td>TNM stage, nuclear grade, performance status</td>
<td>Survival</td>
<td>Algorithm, decision boxes</td>
</tr>
<tr>
<td>UCLA (modified UISS) (47)</td>
<td>2002</td>
<td>Localized, metastatic</td>
<td>All</td>
<td>TNM stage, nuclear grade, performance status, metastasis</td>
<td>Survival</td>
<td>Algorithm, decision boxes</td>
</tr>
<tr>
<td>UCLA (50)</td>
<td>2003</td>
<td>Metastatic</td>
<td>All</td>
<td>Lymph node status, constitutional symptoms, metastasis location, histology, thyroid-stimulating hormone level</td>
<td>Survival</td>
<td>Algorithm</td>
</tr>
<tr>
<td>Mayo Clinic (SSIGN) (51)</td>
<td>2002</td>
<td>Localized, metastatic</td>
<td>Clear cell</td>
<td>TNM stage, tumor size, nuclear grade, histologic necrosis</td>
<td>Survival</td>
<td>Algorithm</td>
</tr>
</tbody>
</table>

MSKCC = Memorial Sloan-Kettering Cancer Center; SSIGN = Stage, Size, Grade, and Necrosis; TNM = tumor, node, metastasis; UCLA = University of California, Los Angeles; UISS = UCLA Integrated Staging System.
algorithm for predicting survival using easily obtainable clinical variables. This model divides patients into subgroups shown to have statistically significant differences in risk of death after nephrectomy (46). The UISS incorporated 1997 TNM stage, nuclear grade, and ECOG performance status into a prognostic model. Using a visual algorithm and decision boxes, patients were stratified into five subgroups with 5-year survival in groups I–V projected at 94%, 67%, 39%, 23%, and 0%, respectively (46).

In a subsequent report, the UISS was modified to identify patients with nonmetastatic or metastatic disease at low, intermediate, or high risk of disease progression (47). This modified UISS has subsequently been validated in larger series of patients by international groups from eight different institutions in four different countries (48). In addition, the UISS system has been used to develop an evidence-based surveillance protocol that provides unique follow-up based on risk stratification (49). Patients considered to be at low risk, according to the UISS staging model, demonstrate rates of recurrence of only 9.6%, with a median time to recurrence of 29 months. Conversely, patients considered to be at high risk manifest a recurrence rate of 58.5%, with a median time to recurrence of 9.5 months (49).

In 2003, the Survival after Nephrectomy and Immunotherapy algorithm was developed to stratify survival of patients with mRCC after nephrectomy and immunotherapy (50). A total of 173 patients with mRCC treated with radical nephrectomy and IL-2 were evaluated, and statistical models were used to determine associations between clinical and pathologic features and survival. A scoring system implementing lymph node status, presence of constitutional symptoms, location of metastases, histology, and thyroid-stimulating hormone was developed to group patients into low-, intermediate-, and high-risk categories. The median survival varied from 5 months for the group identified as high risk to 47 months for the group identified as low risk in this series (50).

**Mayo Clinic Nomogram**

In 2002, investigators at the Mayo Clinic devised the Stage, Size, Grade, and Necrosis (SSIGN) score for patients with clear cell RCC (51). Points are assigned based on 1997 TNM tumor stage, tumor size, nuclear grade, and the presence of histologic necrosis. The estimated CSS for an individual patient at 1–10 years is then estimated based on the total of the SSIGN score. This algorithm was developed based on data from more than 1,800 patients at the Mayo Clinic and has been recently externally validated with a high degree of prognostic accuracy in a series of 388 patients from the kidney cancer database at the University of Verona, Italy (52).

**Adjuvant and Neoadjuvant Trials in Kidney Cancer**

Due to the poor outcomes for patients with advanced disease, studies have been undertaken to determine the potential utility of various forms of adjuvant therapy for those
patients at high risk for recurrent disease. Historically, postoperative adjuvant therapies have not been shown to have clinical benefit for patients with high-risk, locally advanced RCC (Table 3). In spite of this, the initial time after surgical resection holds promise as a period with reduced tumor bulk corresponding with a newly unsuppressed immune system (53).

Published Adjuvant Trials in Renal Cell Carcinoma

In the past, agents that have been studied as adjuvant treatment for high-risk RCC have included radiotherapy, hormonal therapy, and immunotherapy. In a prospective randomized study of radiotherapy versus observation in patients undergoing nephrectomy for stages II and III RCC, there were no differences with regard to relapse rate or survival, and treatments were associated with significant morbidity to abdominal organs (54,55). The use of radiation for RCC is now typically reserved for the palliative treatment of symptomatic bone and central nervous system metastases (56). Hormonal agents, such as medroxyprogesterone acetate, have produced responses in some patients with mRCC due to their ability to block glucocorticoid receptors on some RCC cells; however, when used in an adjuvant setting in 136 patients, there was no improvement in relapse-free survival (RFS) as compared to the observation group (57).

Some small improvements in survival had been reported when IFN is used for mRCC, and trials have been performed examining the use of IFN in the adjuvant setting. Multiple trials have examined the effects of IFN-α for adjuvant therapy after surgery but have been unable to demonstrate a significant benefit in terms of overall survival (OS) or DFS (58). Adjuvant recombinant IFN-α2b was compared with observation after radical nephrectomy in patients with stages II and III renal RCC (59). A total of 247 patients (123 treated) were enrolled in this multicenter, randomized, controlled study. OS probability \( P = .861 \) and probabilities for event-free survival \( P = .107 \) were not found to be significant between treatment and control groups (59).

Other historical studies have attempted to immunize patients against antigens derived from tumor cells to augment the immunologic response. Studies implementing immunotherapy consisting of autologous irradiated tumor cells mixed with bacillus Calmette-Guérin were not able to show a significant difference in OS or DFS (60,61). A multicenter, randomized, controlled phase III trial using high-dose bolus IL-2 after surgery for locally advanced RCC or mRCC was unable to demonstrate any improvement in DFS over observation (62).

The combination of subcutaneous cytokines with the chemotherapeutic agent 5-fluorouracil (5-FU) has shown potentially promising results when used for stage IV mRCC (63). In a recent prospective randomized clinical trial from the German Cooperative Renal Carcinoma Chemoimmunotherapy Group, investigators examined combination immunotherapy and chemotherapy using IL-2, IFN-2α, and 5-FU versus observation in the adjuvant setting for patients at high risk for recurrent RCC (63). At a median follow-
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical setting</th>
<th>Number of participants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation vs. observation (54)</td>
<td>Adjuvant</td>
<td>72</td>
<td>Survival at 26 mo: 50% vs. 62% (NS)</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate vs. observation (57)</td>
<td>Adjuvant</td>
<td>136</td>
<td>Relapse rate: 32.7% vs. 33.9% (NS)</td>
</tr>
<tr>
<td>Tumor cells + bacillus Calmette-Guérin vs. observation (60)</td>
<td>Adjuvant</td>
<td>120</td>
<td>5-yr DFS: 63% vs. 72% (NS)</td>
</tr>
<tr>
<td>Recombinant IFN-α2b vs. observation (59)</td>
<td>Adjuvant</td>
<td>247</td>
<td>5-yr survival probability: 66% vs. 67% (NS)</td>
</tr>
<tr>
<td>IFN-α vs. observation (77)</td>
<td>Adjuvant</td>
<td>283</td>
<td>Median survival: 5.1 vs. 7.4 yr (NS)</td>
</tr>
<tr>
<td>High-dose IL-2 vs. observation (62)</td>
<td>Adjuvant</td>
<td>69</td>
<td>Median DFS: 19.5 vs. 36 mo (NS)</td>
</tr>
<tr>
<td>Tumor cell vaccine (Reniale) vs. observation (64,65)</td>
<td>Adjuvant</td>
<td>558</td>
<td>5-yr PFS: 77.4% vs. 67.8% (P = .02)</td>
</tr>
<tr>
<td>IL-2 + IFN-α2a + FU vs. observation (63)</td>
<td>Adjuvant</td>
<td>203</td>
<td>8-yr DFS: 39% vs. 49% (NS)</td>
</tr>
<tr>
<td>Vitespen (HSPPC-96) vs. observation (69)</td>
<td>Adjuvant</td>
<td>800</td>
<td>Interim analysis: no difference in overall survival/PFS (NS)</td>
</tr>
<tr>
<td>IL-2 + IFN-α2a + FU vs. observation</td>
<td>Adjuvant</td>
<td>550</td>
<td>Phase III completed, results pending</td>
</tr>
<tr>
<td>IL-2 + IFN-α vs. observation (78)</td>
<td>Adjuvant</td>
<td>310</td>
<td>10-yr DFS: 73% vs. 60% (NS)</td>
</tr>
<tr>
<td>Neoadjuvant IL-2 vs. surgery alone (74)</td>
<td>Neoadjuvant</td>
<td>120</td>
<td>5-yr cancer–specific survival: 86% vs. 73% (P = .04)</td>
</tr>
</tbody>
</table>

DFS = disease-free survival; FU = fluorouracil; IFN = interferon; IL-2 = interleukin-2; NS = not significant; PFS = progression-free survival.
up of 4.3 years, OS was significantly decreased after treatment when compared to the control group \( (P = .028) \). Additionally, median RFS was 2.75 years and 4.25 years for the chemoimmunotherapy group and the control group, respectively. Stage-adapted subanalyses similarly revealed no survival advantages of this treatment combination over observation.

Recently, investigators from Germany conducted a multicenter phase III randomized controlled trial using individually prepared autologous renal tumor cell vaccine as adjuvant treatment for patients undergoing radical nephrectomy \((64)\). Patients had stage pT2–3b RCC, with or without lymph node involvement and without distant metastasis. This autologous vaccine (Reniale) was well tolerated and showed a statistically significant survival benefit versus observation. To our knowledge, this is the only adjuvant trial in RCC to date that shows a potential progression-free survival (PFS) advantage. A total of 379 patients were included in the analysis, and 5-year PFS was 77.4% and 67.8% \( (P = .02, \text{log-rank test}) \) for the vaccine group and control group, respectively. It is important to note, however, that 32% of enrolled patients (174 of 553) were lost after randomization, with a disproportionate number of losses from the treatment group (99 vs. 75 from placebo). A criticism of this study, therefore, is that these findings would lose their significance in a true intention-to-treat analysis \((56)\). Additionally, OS was not reported in this initial analysis. A secondary analysis was subsequently performed on 477 patients to include a greater number of patients; this more inclusive intention-to-treat analysis demonstrated a PFS advantage in favor of the treatment group \( (P = .048) \), although OS was not significantly different \( (P = .11) \) \((65)\). Nevertheless, the use of autologous tumor-derived products for patients with high-risk RCC appears promising.

**Ongoing Adjuvant Trials in Renal Cell Carcinoma**

Several trials currently under way examining systemic agents in the adjuvant setting are detailed in Table 4. The European Organisation for Research and Treatment of Cancer (EORTC) has coordinated a phase III adjuvant trial to further evaluate IL-2, IFN-\( \alpha \), and 5-FU for patients with high risk of relapse after surgical treatment for RCC (EORTC protocol 30955). In this study, 550 patients have been randomized to either treatment or observation after surgery. Now closed to recruitment, analysis will determine DFS and OS in each arm \((53)\).

RCC is highly vascular, with disordered angiogenesis. Due to its antiangiogenic effects, thalidomide has been studied in mRCC. A phase III trial for patients with stage IV disease randomized patients to receive IFN-\( \alpha \) with or without thalidomide. This study demonstrated an improvement in PFS using thalidomide \((66)\). Based on these findings, a phase III adjuvant study was initiated at the MD Anderson Cancer Center for patients with high-risk RCC, comparing thalidomide to controls after nephrectomy \((67)\). In a recent interim analysis with 46 patients randomized, there was no difference between groups with regard to DFS, although the treatment group demonstrated significantly
**Table 4.** Current clinical trials of adjuvant and neoadjuvant treatment for renal cell carcinoma (RCC)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Study group</th>
<th>Placebo</th>
<th>Treatment duration</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Rencarex Immunotherapy Phase III Trial to Study Efficacy</td>
<td>Adjuvant</td>
<td>G250 mAb</td>
<td>Yes</td>
<td>54 wk</td>
<td>Clear cell RCC</td>
</tr>
<tr>
<td>in Non-metastatic Renal Cell Carcinoma (ARISER)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence of M+ disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Meets stage criteria:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage T3b/c N0/X or T4 N0/X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any T stage with N+ disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1b N0/X or T2 N0/X with microscopic vascular invasion and grade ≥ III or T3a N0/X and grade ≥ III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence of residual disease</td>
</tr>
<tr>
<td>Adjuvant Sunitinib, Sorafenib for Unfavorable Renal Cell Carcinoma</td>
<td>Adjuvant</td>
<td>Sunitinib,</td>
<td>Yes</td>
<td>1 yr</td>
<td>Clear cell and non-clear cell tumors</td>
</tr>
<tr>
<td>(ASSURE)</td>
<td></td>
<td>sorafenib</td>
<td></td>
<td></td>
<td>Stage T2-4 and stage T1b with high grade (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nx, N0, N1, or N2 if all positive nodes removed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence of M+ disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence of residual or recurrent disease</td>
</tr>
<tr>
<td>Sorafenib for Patients with Resected Primary Renal Cell Carcinoma</td>
<td>Adjuvant</td>
<td>Sorafenib</td>
<td>Yes</td>
<td>3 yr</td>
<td>Clear cell and non-clear cell tumors</td>
</tr>
<tr>
<td>(SORCE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intermediate- or high-risk disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No evidence of residual macroscopic disease after resection</td>
</tr>
<tr>
<td>Trial</td>
<td>Treatment</td>
<td>Adjuvant</td>
<td>Phase</td>
<td>Duration</td>
<td>Disease Characteristics</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>----------</td>
<td>-------</td>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Sunitinib Trial in Adjuvant Renal Cancer (STAR)</td>
<td>Adjuvant</td>
<td>Sunitinib</td>
<td>Yes</td>
<td>High-risk RCC per University of California, Los Angeles Integrated Staging System criteria</td>
<td>No prior systemic therapy</td>
</tr>
<tr>
<td>Phase II Single Arm Prospective Study of Neoadjuvant Sutent (University Health Network, Toronto)</td>
<td>Neoadjuvant</td>
<td>Sunitinib</td>
<td>No</td>
<td>12 wk</td>
<td>Clear cell RCC, Clinical stage T1a or T1b, No evidence of nodal or metastatic disease, No prior therapy of any kind for RCC</td>
</tr>
<tr>
<td>Phase II Prospective Study of Neoadjuvant Sorafenib (University of North Carolina)</td>
<td>Neoadjuvant</td>
<td>Sorafenib</td>
<td>No</td>
<td>8 wk</td>
<td>Radiographic RCC, Stage II or higher, May have N+ or M+ disease, Not yet undergone nephrectomy</td>
</tr>
</tbody>
</table>

N = node; M = metastasis; T = tumor.
better CSS compared to observation (56). Additionally, patients in the treatment arm of this study have experienced significant toxicity requiring dose reductions and early termination of therapy (56). This study closed due to poor accrual.

One novel approach toward treatment of RCC focuses on heat shock proteins (HSPs), ubiquitous molecules that function to protect living cells from injury and stress. HSPs can inhibit apoptosis in tumor cells and can act as foreign antigens to elicit an immune response and subsequent cell destruction (53,68). Vaccines have been developed that consist of HSP-peptide complexes isolated from a patient's tumor. After vaccination, antigenic tumor peptides induce a much more potent antitumor immune response than the tumor itself (53). The largest phase III adjuvant clinical trial has been completed evaluating the vaccine HSPPC-96 (Vitespen®, Antigenics, Inc., New York, NY) as adjuvant therapy for high-risk, non-mRCC. In this study, 818 patients enrolled at 145 international clinical sites have been randomized to surgical extirpation, followed by treatment with HSPPC-96 or surgery alone. Although final results of this trial are pending, interim analysis failed to show a significant difference between the observation and treatment groups with regard to DFS or OS (56). However, early analysis does demonstrate an apparent benefit in a subset of patients with better prognostic factors—a group correlating with “intermediate risk” patients (69).

Another currently ongoing clinical trial involves the use of a monoclonal antibody against G250, a transmembrane protein associated with RCC, which is identical to CA IX (70). cG250 (WX-G250, Rencarex®, Wilex Pharmaceuticals, Munich, Germany) is a monoclonal immunoglobulin G1 antibody administered intravenously that binds to CA IX on clear cell RCC and may recruit effector cells or activate complement to result in cell death (53). In 2004, an international randomized, phase III trial, ARISER (Adjuvant Rencarex Immunotherapy trial to Study Efficacy in nonmRCC), opened to accrual to evaluate cG250 versus placebo after nephrectomy for 612 patients with high-risk non-metastatic clear cell RCC (53,67). This trial is currently accruing with a goal of 1,332 patients.

Sorafenib (Nexavar®, Bayer HealthCare Pharmaceuticals, Wayne, NJ) is an orally available, small-molecule inhibitor of RAF kinase that competitively binds to the ATP binding site of some kinases in the RAF family relevant to RCC. In this way, sorafenib inhibits the signaling pathway mediating tumor cell proliferation and angiogenesis (67). Data support an inhibitory effect of sorafenib on angiogenesis in human studies (71). Several clinical trials using sorafenib have demonstrated efficacy in mRCC, including studies for cytokine-refractory disease and combination studies with cytokines (67). Sunitinib (Sutent®, Pfizer Pharmaceuticals, New York, NY) is an oral TKI, which has been shown to be superior to IFN in the management of mRCC (72). Both agents have recently received U.S. Food and Drug Administration approval and are marketed for the management of patients with mRCC. On this basis, a phase III trial is currently under way, randomizing patients to receive either sorafenib, sunitinib, or a placebo after definitive surgery. The study, named A.S.S.U.R.E. (adjuvant sorafenib sunitinib for unfavorable renal cell carcinoma) is sponsored by ECOG. Eligible patients will have locally advanced nonmetastatic
Adjuvant and Neoadjuvant Therapy for Renal Cell Carcinoma

Disease with or without lymph node involvement, with PFS as the primary end point. Patients may be registered for this trial based on unfavorable pathologic findings after surgical resection or preoperatively based on high-risk radiographic findings, thus allowing for tissue correlative studies. Secondary end points include OS and toxicity in the adjuvant setting. Another phase III trial examining the use of sorafenib in the adjuvant setting, sponsored by the Medical Research Council, is currently under development. SORCE (sorafenib for patients with resected renal cell carcinoma) is a randomized controlled study comparing sorafenib administered for 3 years, or 1 year with placebo, in patients with resected primary RCC at high or intermediate risk of relapse. This study aims to recruit approximately 331 patients per year for each of 5 years, with an additional 3 years of follow-up. The primary end point is metastasis-free survival, and secondary measures include CSS, OS, cost effectiveness, and toxicity. This study is not yet open. The ongoing clinical trials of adjuvant therapy for high-risk RCC patients are summarized in Table 4. The STAR (sunitinib trial in adjuvant renal cancer) trial is a randomized, double-blind, phase III study comparing adjuvant sunitinib versus placebo for patients classified as high risk, according to the UISS, after surgical resection. The primary end point in this study is DFS, and secondary end points include RFS as well as OS.

Neoadjuvant Strategies for Localized Renal Cell Carcinoma

The notion of administering systemic therapy for RCC before surgical extirpation remains somewhat controversial. The benefits of neoadjuvant therapy include the ability to assess resected tissue for treatment effect and possible improvements in survival end points, resulting from the treatment administered before surgery. However, these potential benefits must be balanced against the risks that preoperative systemic therapy may lead to increased perioperative morbidity and may even delay the timing of surgery (56). Thus, though a few nonrandomized studies have addressed the issue of neoadjuvant therapy before surgical extirpation, prospective studies are generally lacking. In a retrospective analysis of 71 patients with clinically localized RCC, no clear advantage in RFS was seen for 17 patients who received preoperative IFN, with or without tumor embolization (88.9% and 71.4% RFS, respectively), as compared to those not receiving neoadjuvant treatment (94.9% RFS) (73). However, it should be noted that significant differences in tumor characteristics and duration of follow-up existed among groups in this retrospective analysis. Recently, investigators in Germany reported their results from a nonrandomized controlled phase II trial to investigate the role of perioperative immunomodulation by means of a short course of preoperative IL-2 in patients with RCC undergoing nephrectomy (74). In this study, recombinant human IL-2 was administered subcutaneously for 6 days, starting 1 week before the date of planned surgery. A significant improvement in 1- and 5-year CSS was seen for patients in the IL-2 group (98% and 86%) versus the control group (81% and 73%), with a similar effect for PFS (74). Randomized, phase III data have not yet been reported.
Adjuvant and Neoadjuvant Therapy for Renal Cell Carcinoma

The role of preoperative tumor embolization as a means of neoadjuvant therapy, before nephrectomy, has been examined. The benefit of embolization is presumed to be the systemic release of tumor antigens after embolization with subsequent immunologic effects (56). Indeed, a nonrandomized retrospective study suggested some survival benefit (62% vs. 35% 5-year OS) resulting from preoperative embolization, although prospective confirmation of these findings has not yet been reported (75).

Several phase II trials utilizing TKIs in the neoadjuvant setting are scheduled to open in 2007. A single-arm, open-label, prospective study examining the neoadjuvant use of sunitinib for RCC is scheduled to open in late 2007. In this phase II study, examiners at the University Health Network, Toronto, will administer two cycles of sunitinib to patients with clinical stage T1a or T1b, biopsy-proven, clear cell RCC before surgical resection. The primary end point in this study is radiographic response, with an accrual goal of 30 patients. A study at the University of North Carolina is recruiting a total of 30 patients to participate in a phase II trial of neoadjuvant sorafenib for stage II or higher RCC. As novel therapies demonstrate efficacy in the metastatic setting, studies such as these hold promise that treatments may be applied to the adjuvant and neoadjuvant settings.

Summary

The standard of care for clinically localized RCC remains surgical resection due to the favorable prognosis associated with surgery and the relative ineffectiveness of systemic therapy alone. Prognostic variables have been integrated into predictive algorithms to better identify patients at risk for disease recurrence. Molecular and genetic markers may improve the ability to perform such risk stratification. Due to the poor outcomes for patients with advanced disease, studies have been undertaken to determine the role of various forms of adjuvant therapy for high-risk disease. Although adjuvant therapies in RCC have not yet been shown to be effective, a better understanding of the molecular and cellular biology of this cancer has led to the development of several promising systemic targeted anticancer agents that are currently involved in clinical trials. Investigation of molecular and genetic tumor markers may help to identify additional cellular targets for future adjuvant or neoadjuvant therapies for RCC.

References


CME Post-Test

1. In renal cell carcinoma (RCC) patients, $^{18}$F fluorodeoxyglucose positron emission tomography imaging adequately characterizes small metastatic lesions; in addition, the test is predictive for the presence of RCC in imaged lesions.

   a) True
   b) False

2. In treating metastatic RCC with clear cell histology, the standard of care is:

   a) Sorafenib (Nexavar).
   b) Interleukin-2–based systemic immunotherapy.
   c) Upfront cytoreductive nephrectomy.
   d) Active surveillance with delayed treatment.

3. A subtype of RCC that accounts for 10%–15% of all cases, has a 5-year survival approaching 90%, and that more commonly features bilateral and multifocal tumors than do other RCC subtypes is the:

   a) Papillary type.
   b) Chromophobe type.
   c) Medullary type.
   d) Multilocular cystic type.

4. Which of the following statements is true?

   a) All specimens should be fixed in formalin immediately after excision.
   b) Approximately 8%–12% of renal tumors remain unclassified using the current World Health Organization classification.
   c) The Fuhrman grading system is an independent prognostic predictor for clear cell RCC and RCC, not otherwise specified.
   d) Fuhrman grades can be grouped into low grade (grades 1 and 2), intermediate grade (grade 3), and high grade (grades 4 and 5).

To earn CME credit at no cost, please visit us online at www.cancernetwork.com/cme
5. Maladzys et al. analyzed data from 181 patients with various stages of metastatic RCC, finding that improved survival correlated with:
   a) Longer disease-free intervals between nephrectomy and time of metastasis.
   b) Age <55 years.
   c) Prior cytotoxic chemotherapy.
   d) All of the above.

6. A factor that predicts rapid progression of RCC under cytokine therapy is:
   a) The presence of hepatic metastases.
   b) Elevated neutrophil counts.
   c) A short interval from renal tumor to metastases (<1 year).
   d) All of the above.

7. A phase III, randomized, multicenter study of RCC patients with poor prognosis by Hudes et al. found a longer overall survival among patients in which of the following arms?
   a) 3 MU (million units) of interferon (IFN)-α (escalation up to 18 MU as tolerated) subcutaneously three times weekly.
   b) 25 mg of temsirolimus (Torisel) intravenously weekly.
   c) Combined use of 15 mg of temsirolimus plus 6 MU of IFN-α three times weekly.
   d) There was no difference in overall survival among the three arms.

8. Hand–foot syndrome (palm-plantar erythrodysesthesia) is a major adverse reaction related to which of the following drugs?
   a) Temsirolimus.
   b) Sorafenib.
   c) GW-786034 (pazopanib).
   d) AG-013736 (axitinib).

9. Which of the following statements is true?
   a) Therapy with mammalian target of rapamycin (mTOR) inhibitors may be most effective against RCCs having an abnormally inactivated mTOR pathway.
   b) Everolimus is the standard of care for patients with poor-risk features and those with non–clear cell RCC.
   c) Thalidomide has very modest activity in metastatic RCC; its use is not favored in the vast majority of patients with this disease.
   d) None of the above.

To earn CME credit at no cost, please visit us online at www.cancernetwork.com/cme
10. To date, the most significant molecular marker for RCC is:
   a) Gelsolin.
   b) Carbonic anhydrase IX.
   c) Ep-CAM.
   d) p53.

To earn CME credit at no cost, please visit us online at www.cancernetwork.com/cme
Index

Note: Page numbers followed by *t* indicate tables; those followed by *f* indicate figures.

A
Ablative techniques, 9–10, 116
cryoablation, 9–10
radiofrequency, 9, 10
surveillance after, 13t
Active surveillance, 10
Adenoma, papillary, 29
Adjuvant Rencarex Immunotherapy
   Phase III Trial to Study Efficacy in Non-metastatic Renal Cell Carcinoma (ARISER), 69, 128t, 130
Adjuvant Sorafenib Sunitinib for Unfavorable Renal Cell Carcinoma (ASSURE) trial, 128t, 130–131
Adjuvant therapy trials, 125–131
   completed or historical, 125–127, 126t
   ongoing, 127–131, 128t–129t
Adrenal involvement, 6
   as prognostic factor, 37t, 38, 54t, 118t
   and role of routine adrenalectomy, 7
   staging of, 5t, 6, 36t, 120
Adrenalectomy, routine, role in radical nephrectomy, 7
Advanced RCC
   endothelin inhibition in, 105–106
   everolimus in, 100–102
   extracellular matrix protein inhibition in, 107–109
   interferon-α therapy in, 65–66
   interleukin-2 therapy in, 62–64
   lenalidomide in, 104–105
   multi-targeted kinase inhibitors in, 73–91
   nuclear factor κB inhibitors in, 106–107
   sorafenib in, 74–81
   sunitinib in, 81–85
   temsirolimus in, 102–103
   thalidomide in, 103–104
   vaccines in, 66–68
   vascular endothelial growth factor as therapy target in, 95–100
Advanced Renal Cell Carcinoma Sorafenib (ARCCS) study, 80–81
AG-013736 (axitinib), 55, 73, 86–87, 86t
Akt, 97f, 100
   and phosphoinositide 3-kinase signaling pathway, 22, 23f, 48, 54–55
American Joint Committee on Cancer staging system, 4–6, 5t, 120
   surveillance guidelines based on, 12t–13t
Angiogenesis
   inhibitors of, 47, 66
   vascular endothelial growth factor in, 47, 96
Angiography in RCC, 3–4
Anti-vascular endothelial growth factor antibodies, 95–100
Antihypertensive agents in multi-targeted kinase inhibitor therapy, 89, 90t
ARCCS (Advanced Renal Cell Carcinoma Sorafenib) study, 80–81
ARISER study, 69, 128t, 130
ASSURE trial, 128t, 130–131
Atrasentan, 106
Axitinib, 55, 73, 86–87
adverse effects of, 87, 86t
Azacitidine, 65t
B
Bacillus Calmette-Guérin in adjuvant therapy, 125, 126t
Bellini collecting duct carcinoma, 27t
Bevacizumab, 55, 61, 96–100
adverse effects and toxicity of, 96
with erlotinib, 97–98
with interferon-α, 66, 98–99
with interleukin-2, 99
mechanism of action, 23f, 24, 47, 96, 97f
ongoing trials on, 65t
phase II trials on, 65t, 96
response to, 96
with sorafenib, 99
with sunitinib, 99
with temsirolimus, 99, 100
BHD gene, 26
Biopsy, percutaneous renal, 4
Birt-Hogg-Dube syndrome, 20
chromophobe RCC in, 25, 26
renal oncocytoma in, 29, 30
Bone metastasis of RCC, 40, 54t
Bortezomib, 106–107
C
Cachexia as prognostic indicator, 45, 120
Calcium serum levels as prognostic indicator, 120
in Memorial Sloan-Kettering Cancer Center model, 50, 50f, 51
Carbonic anhydrase IX, 22
as prognostic factor, 46–47, 63–64, 120–121
in interleukin-2 therapy, 47, 63–64
as therapy target, 69
CCI-779, 102–103. See also Temsirolimus
Cetuximab, 23f
Chromophobe RCC, 25–26, 115
prognosis in, 41, 41t, 42, 43, 120
tumor necrosis in, 43
Chromosome abnormalities, 19, 20
in chromophobe RCC, 26
in clear cell RCC, 21–22
in papillary adenoma, 29
in papillary RCC, 25
in renal oncocytoma, 30
in uncommon RCC subtypes, 27t–28t
Xp11.2 translocation, 19, 28t
Classification of RCC, 19–20, 20t
Clear cell RCC, 11, 20–24, 41, 115
carbonic anhydrase IX in, 46, 63–64
epidemiology of, 20, 41
hypoxia-inducible factor in, 22, 23f, 46
immunotherapy in, 61–69
multi-targeted kinase inhibitors in, 73–91
poorly differentiated, 21
prognosis in, 41, 42, 43
Mayo Clinic SSIGN score on, 51–52
prediction models on, 63–64
sarcomatoid differentiation in, 21
tumor necrosis in, 43
vascular endothelial growth factor in, 22, 23f, 24, 47
Clinical features of renal cell neoplasms, 2, 3t
in chromophobe RCC, 25
in clear cell RCC, 20–21
in oncocytoma, 29
Index 143

in papillary adenoma, 29
in papillary RCC, 24
and prognosis, 44–45, 54t, 117, 118t, 120
in uncommon subtypes, 27t–28t
Collecting duct carcinoma, 27t, 115
prognosis in, 41, 41t, 43, 120
Computed tomography in RCC, 3, 7
and energy-based tissue ablation, 9, 10
CpG island methylation as prognostic indicator in RCC, 121
Cryoaulation in RCC, 9–10
Cyclin-dependent kinase inhibitors as prognostic factor, 48
Cytokine Working Group, 63, 64
ongoing trials, 64, 65t
Cytokines as prognostic factor in RCC, 48–49

D
Dendritic cell vaccines, 66, 68t
Denileukin difftox, 65t
Diagnosis of RCC, 2–4
specimen handing in, 31–32
Diarrhea in axitinib therapy, 87, 86t
management of, 89
in pazopanib therapy, 87, 88t
in sorafenib therapy, 77, 78, 78t, 79, 81
in sunitinib therapy, 83, 85t, 87–88
DNA methylation patterns as prognostic indicator in RCC, 121
Doppler imaging in RCC, 4

E
Eastern Cooperative Oncology Group (ECOG) performance status, 40, 42–43, 44–45, 117
in UCLA Integrated Staging System, 52, 53f
Embolization in neoadjuvant therapy, 132
Endothelins, 105–106
inhibitors of, 106
Energy-based tissue ablation in RCC, 9–10, 116
cryoaulation in, 9–10
radiofrequency ablation in, 9, 10
surveillance after, 13t
Ep-CAM as prognostic indicator in RCC, 121
Epidemiology of renal cell neoplasms, 1
in chromophobe RCC, 41
in clear cell RCC, 20, 41
in oncocytoma, 29
in papillary adenoma, 29
in papillary RCC, 24, 41
Epidermal growth factor receptor inhibitor, erlotinib as, 97–98
Erlotinib, 97–98
with bevacizumab, 97–98
mechanism of action, 23f, 24
Erythrodysesthesia, palmo-plantar. See Hand–foot syndrome
European Organisation for Research and Treatment of Cancer (EORTC) trials on adjuvant therapy, 127
on interferon therapy and nephrectomy, 13
on lymphadenectomy, 8, 39
Everolimus, 100–102
Extracellular matrix protein inhibition, 107–109

F
Fatigue in axitinib therapy, 87, 86t
in interferon therapy, 99
management of, 87–89
in pazopanib therapy, 87, 88t
in sorafenib therapy, 77, 78, 79, 81
in sunitinib therapy, 83, 85t, 87–88
Fatty tissue involvement as prognostic factor, 37t, 38, 54t, 118t
staging of, 5t, 36t
FH gene, 25
FHIT, 22
Fluorodeoxyglucose positron emission tomography, 4
5-Fluorouracil in adjuvant therapy, 125, 126t, 127
Foliculin, 26
Follow-up strategies, risk-based, 11
French Immunotherapy Intergroup trials, 64–66
Fuhrman grading system, 29, 31
and prognosis in RCC, 31, 40, 120
in UCLA Integrated Staging System, 52, 53f
Fumarate hydratase gene in papillary RCC, 25

G
Gefitinib, 23f, 65t
Gelsolin as prognostic factor in RCC, 121
Genetic factors in renal cell neoplasms, 1
in chromophobe RCC, 26
in classification criteria, 19–20
in clear cell RCC, 21–24, 23f
in papillary adenoma, 29
in papillary RCC, 25
in renal oncocytoma, 30
in uncommon subtypes, 27t–28t
Genistein, 65t
Grading system of Fuhrman, 29, 31
and prognosis in RCC, 31, 40, 120
in UCLA Integrated Staging System, 52, 53f
Fumarate hydratase gene in papillary RCC, 25

H
Hair color changes in pazopanib therapy, 87, 88t
Hand–foot syndrome
management of, 89
in pazopanib therapy, 88t

Heat-shock protein-peptide complex (HSPPC-96) vaccine, 67, 69, 126t, 130
Hemoglobin levels as prognostic indicator, 120
in Memorial Sloan-Kettering Cancer Center model, 50, 50f, 51
Histologic features in RCC, 115
and prognosis, 40–44, 41t, 54t, 118t, 120
HSPPC-96 (heat-shock protein-peptide complex) vaccine, 67, 69, 126t, 130
Hypertension
in axitinib therapy, 87, 86t
in bevacizumab therapy, 96, 99
in interferon therapy, 99
management of, 90t, 89
in pazopanib therapy, 87, 88t
in sorafenib therapy, 77, 77f, 78, 88
incidence of, 78t, 79, 81
in sunitinib therapy, 83, 85t
Hypoxia-inducible factor (HIF), 100
in clear cell RCC, 22, 23f, 46
interaction with VHL protein, 22, 46, 48
in papillary RCC, 25
as prognostic indicator, 45–46, 47, 48
upstream mediators of, 48
Hypoxia-response elements (HREs), 46

I
Immunomodulatory agents, 103–105
lenalidomide, 104–105
thalidomide, 103–104
Immunotherapy, 13, 61–69
biologic basis of, 61–62
interferon-α in, 64–66
interleukin-2 in, 62–64
in lymph node involvement, 39
ongoing trials on, 65t, 68t
prediction of response to, 49–51
vaccines in, 66–68
Inflammatory response as prognostic factor, 41t
Integrated Staging System of UCLA, 6, 11, 52, 53f, 122–124, 123t
Integrins, 107–109
Interferon-α therapy, 64–66, 69
  adverse effects and toxicity in, 99
  with bevacizumab, 66, 98–99
  with interleukin-2 therapy, 63, 64, 126t
  and nephrectomy, 66, 122, 125, 126t, 127
  ongoing trials on, 65t, 127
  pegylated, 66
  response to, 64–66
  prediction of, 50–51, 122
  sorafenib therapy compared to, 79–80
  sunitinib therapy compared to, 66, 83, 85t
  with temsirolimus, 102–103
  temsirolimus therapy compared to, 66, 102–103
Interleukin-2 therapy, 13, 42, 61, 62–64, 69
  with bevacizumab, 99
  and carbonic anhydrase IX expression, 47, 63–64
  with interferon-α therapy, 63, 64, 126t
  and nephrectomy, 125, 126t, 127, 131
  ongoing trials on, 65t
  response to, 62–63, 69
  prediction of, 52
  in sarcomatoid features, 44
  survival rates in, 124
  toxicity of, 62, 99
Interleukin-4 as prognostic factor in RCC, 49
International Union against Cancer, 41, 120
Ipilimumab, 69

K
Karnofsky performance status, 117
  in Memorial Sloan-Kettering Cancer Center prediction model, 50, 50f, 51
Ki67 as prognostic indicator in RCC, 121

L
Laboratory evaluation in RCC, 3
  in surveillance guidelines, 12t–13t
Lactate dehydrogenase serum levels, 50, 50f
Laparoscopy
  cryoablation in, 10
  radical nephrectomy in, 7
Leiomyomatosis, hereditary, and RCC syndrome, 25
Lenalidomide, 104–105
  adverse effects and toxicity of, 105
  mechanism of action, 104, 105
  response to, 105
Lung metastasis of RCC, 40
Lymph node involvement in RCC
  dissection in, 7–8, 31, 39
  prognosis and survival rates in, 37t, 39, 54t, 116–117, 118t, 120
  staging of, 5t, 36t, 120
Lymphadenectomy, 7–8
  specimen handling in, 31
  survival rates in, 39

M
M200 (volociximab), 108–109
Magnetic resonance imaging in RCC, 3, 7
  and energy-based tissue ablation, 9, 10
Mammalian target of rapamycin (mTOR), 48, 54–55, 73
  in clear cell RCC, 22, 23f, 24
  inhibitors of, 100–103
  everolimus, 100–102
  temsirolimus, 102–103
  signaling pathway, 101f
Mayo Clinic stage, size, grade, and necrosis (SSIGN) score, 6, 51–52, 123t, 124
Medroxyprogesterone acetate
  completed trials on, 125, 126t
  response to, 64, 104
Medullary carcinoma, 27t, 115
Memorial Sloan-Kettering Cancer Center
prognostic models on RCC, 6, 
49–51, 50f, 122, 123t

c-met proto-oncogene, 1, 25
Metastasectomy, 14
Metastasis of RCC
to bone, 40, 54t
carbonic anhydrase IX in, 47
do
do
endothelin inhibition in, 105–106
everolimus in, 100–102
extracellular matrix protein inhibition in, 107–109

immunomodulatory agents in, 103–105
immunotherapy in, 61–69

lenalidomide in, 104–105
to lung, 40
mammalian target of rapamycin inhibitors in, 100–103
multi-targeted kinase inhibitors in, 73–91

nuclear factor κB inhibitors in, 106–107
prognosis and survival rates in, 37t, 39, 40, 54t, 116–117, 118t, 120
prediction of, 51, 53, 53f, 63–64

in radical nephrectomy, 5
staging of, 5t, 36t, 120
surgery in, 5, 11–14

adrenalectomy in, 7

lymphadenectomy in, 7–8

surveillance for
active, in watching waiting approach, 10
in risk-based follow-up strategies, 11
temsirolimus in, 102–103
thalidomide in, 103–104

UCLA Integrated Staging System in, 124
vascular endothelial growth factor as therapy target in, 95–100

Methylation patterns as prognostic indicator, 121

Microvascular invasion as prognostic factor, 41t, 44

Mucin ous tubular spindle cell carcinoma, 28t
Mucositis, management of, 89–90
Multi-targeted tyrosine kinase inhibitors, 73–91

adverse effects and toxicity of, 87–91

axitinib, 55, 73, 86–87
indications for, 91

pazopanib, 73, 87

sorafenib, 74–81. See also Sorafenib

sunitinib, 81–85. See also Sunitinib

Multilocular cystic RCC, 27t

N
Necrosis, tumor

in Mayo Clinic stage, size, grade, and necrosis (SSIGN) score, 6, 51–52, 124

as prognostic factor, 41t, 42–43, 120

Neoadjuvant therapy, 14, 131–132
completed trials on, 126t

current trials on, 129t

Nephrectomy, 6–8

and adjuvant therapy, 125–131

and adrenalectomy, 7

and interferon-α therapy, 66, 122, 125, 126t, 127

and interleukin-2 therapy, 125, 126t, 127, 131

laparoscopic, 7

and lymphadenectomy, 7–8

in metastatic RCC, 11–14, 116–117

and neoadjuvant therapy, 14, 126t, 131–132

nephron-sparing, 8–9, 116
indications for, 9, 36–37

surveillance guidelines after, 12t

tumor size in, 9, 36–37, 116

prognosis and survival rates in, 5, 7, 117–124

Mayo Clinic SSIGN score on, 51–52, 124
Memorial Sloan-Kettering Cancer Center nomogram on, 122
recurrence risk in, 122–124
UCLA Integrating Staging System on, 122–124
radical. See Radical nephrectomy recurrence in, 8–9, 117
risk for, 122–124
specimen handling in, 31
surveillance after, 11, 12t–13t
Nephron-sparing surgery in RCC, 8–9
indications for, 9, 36–37
surveillance guidelines after, 12t
tumor size in, 9, 36–37, 116
Neuroblastoma, RCC associated with, 28t
Nexavar®. See Sorafenib
Nuclear factor-κB inhibitors, 106–107
Nuclear grading system, 31
as prognostic factor, 31, 40, 41t
O
Oncocytes in renal oncocytoma, 30
Oncocytoma, renal, 29–30
Oncophage®, 67, 68t, 69
P
p21, 48
p27, 48
p53, 121
Papillary adenoma, 29
Papillary RCC, 24–25, 115
epidemiology of, 24, 41
in hereditary syndrome, 25
prognosis in, 41, 41t, 42, 43, 47
tumor necrosis in, 43
type 1, 24, 25, 41t, 42
type 2, 24, 25, 41t, 42
vascular endothelial growth factor in, 47
Paraneoplastic syndromes in RCC, 2, 3t
prognosis in, 41t, 45
Pathology in renal cell neoplasms
in chromophobe RCC, 25–26, 26f
in classification criteria, 19–20
in clear cell RCC, 21, 21f
in papillary adenoma, 29
in papillary RCC, 24f, 24–25
in renal oncocytoma, 30, 30f
in uncommon subtypes, 27t–28t
Pazopanib, 73, 87
adverse effects of, 88t, 87
Performance status as prognostic factor, 41t, 44–45, 117, 120
in Memorial Sloan-Kettering Cancer Center model, 50, 50f, 51
in UCLA Integrated Staging System, 52, 53f
Perinephric fat involvement as prognostic factor, 37t, 38
staging of, 5t, 36t
Phase II Prospective Study of Neoadjuvant Sorafenib, 129t
Phase II Single Arm Prospective Study of Neoadjuvant Sutent, 129t
Phosphoinositide 3-kinase, 22, 23f, 48, 54–55, 97f
Physical examination in RCC, 3
Positron emission tomography in RCC, 4
Prediction models on RCC, 49–52
of Mayo Clinic, 6, 51–52, 123t, 124
of Memorial Sloan-Kettering Cancer Center, 6, 49–51, 50f, 122, 123t
of University of California at Los Angeles, 6, 11, 52, 53f, 122–124, 123t
Preoperative therapy for RCC, 14, 131–132
completed trials on, 126t
current trials on, 129t
Prognosis and survival in RCC, 5–6, 7, 35–55, 54t, 117–124
in adrenal involvement, 37t, 38, 54t, 118t
in chromophobe type, 42
in clear cell type, 42
in fatty tissue involvement, 37t, 38, 54t, 118t
148  Index

Prognosis and survival in RCC,—Cont.
in Fuhrman grading system, 31, 40, 120
histologic features affecting, 40–44,
41t, 54t, 118t, 120
hypoxia-inducible factor affecting, 45–
46, 47, 48
in integrated prediction models, 49–52
in lymph node involvement, 37t, 39,
54t, 116–117, 118t, 120
in Mayo Clinic SSIGN score, 6, 51–
52, 123t, 124
in Memorial Sloan-Kettering Cancer
Center model, 6, 49–51, 50f,
122, 123t
in metastasis, 37t, 39, 40, 118t
in papillary type, 24, 25, 42
and radical nephrectomy, 7, 8, 124
in recurrence risk after surgery, 122–124
in risk-based follow-up strategies, 11,
12t–13t
in sarcomatoid differentiation, 31,
41t, 43–44, 120
stage affecting, 116f, 116–117
tumor size affecting, 6, 35–38, 37t,
54t, 118t, 120
in UCLA Integrated Staging System, 6,
11, 52, 53f, 122–124, 123t
in venous involvement, 37t, 38–39, 118t
Proteinuria
in axitinib therapy, 87, 86t
in bevacizumab therapy, 96, 99
in interferon therapy, 99
PTEN, 100
as prognostic factor in RCC, 48, 54–
55, 121
lymph node dissection in, 7–8
metachronous contralateral tumor
development after, 8–9
stage and survival in, 5, 7, 116, 124
surveillance after, 12t
Radiofrequency ablation in RCC, 9, 10
Radiologic evaluation in RCC, 3–4
in surveillance guidelines, 12t–13t
Rapamycin, mammalian target of
(mTOR). See Mammalian target
of rapamycin (mTOR)
Recurrence of RCC, 8–9, 117
risk for, 122–124
surveillance for, 11
Renal sinus fat involvement
as prognostic factor, 37t, 38, 118t
staging of, 5t, 36t
Renal vein involvement
as prognostic factor, 37t, 38–39
staging of, 5t, 36t
Rencarex® immunotherapy, 69, 128t, 130
Rhabdoid cells in clear cell RCC, 21
Risk-based follow-up strategies, 11
S
Sarcomatoid RCC, 21, 30–31
prognosis in, 31, 41t, 43–44, 120
Signs and symptoms in RCC. See Clinical
features of renal cell neoplasms
Size of tumor
in Mayo Clinic SSIGN score, 6, 51–
52, 124
in nephron-sparing surgery, 9, 36–37,
116
as prognostic factor, 6, 35–38, 37t,
54t, 118t, 120
Sorafenib, 55, 73, 74–81
in adjuvant therapy, 128t, 130–131
adverse effects and toxicity of, 77f,
77–78, 78t, 87–91
in ARCCS study, 81
compared to interferon, 79
with bevacizumab, 99
interferon therapy compared to, 79–80
mechanism of action, 23f, 24, 74, 75t, 97f
in neoadjuvant therapy, 129t
ongoing trials on, 65t
phase II randomized discontinuation trial on, 74–75
phase III placebo-controlled trial on, 76t, 76–79
phase IV ARCCS trial on, 80–81
response to, 13, 61, 78–79, 79f, 80f, 81f
Sorafenib for Patients with Resected Primary Renal Cell Carcinoma (SORCE), 128t, 131
Southwest Oncology Group (SWOG) trials, 13, 65t, 66
Specimen handling and preparation in RCC, 31–32
Spindle cell carcinoma, mucinous tubular, 28t
SSIGN (stage, size, grade, and necrosis) score, 6, 51–52, 123t, 124
Staging of RCC, 4–6, 5t
in Mayo Clinic SSIGN score, 6, 51–52, 123t, 124
and nephron-sparing surgery, 9
and prognosis, 5–6, 35–39, 37t, 120
and risk-based follow-up strategies, 11, 12t–13t
and survival rates, 116f, 116–117
in UCLA Integrated Staging System, 6, 11, 52, 53f, 122–124
STAR trial, 129t, 131
Stem cell transplantation, 69
Stomatitis
in axitinib therapy, 86t
in sunitinib therapy, 85t
Sunitinib, 73, 74, 81–85
in adjuvant therapy, 128t, 129t, 130–131
adverse effects and toxicity of, 87–91
in phase III trial, 83, 85t
with bevacizumab, 99
expanded access trial on, 83–85
interferon therapy compared to, 66, 83, 85t
mechanism of action, 23f, 24, 81–82, 82t, 97f
in neoadjuvant therapy, 129t, 132
phase II trials on, 83
phase III trial on, 14, 83
adverse effects in, 83, 85t
response to, 13, 55, 61, 83
tumor shrinkage in, 84f
Sunitinib Trial in Adjuvant Renal Cancer (STAR) trial, 129t, 131
Surgical management of RCC, 2, 6–14, 115–132
adrenalectomy in, 7
energy-based tissue ablation in, 9–10, 116
lymphadenectomy in, 7–8, 31, 39
in metastasis, 11–14
nephrectomy in. See Nephrectomy
Surveillance
active, and watchful waiting in RCC, 10
in risk-based follow-up strategies, 11, 12t–13t
Surveillance, Epidemiology, and End Results (SEER) database, 8–9
Survival rates in RCC. See Prognosis and survival in RCC
T
TARGET trial on sorafenib, 76t, 76–79, 88
adverse effects in, 77f, 77–78, 78t
tumor shrinkage in, 80f
Temsirolimus, 73, 102–103
adverse effects and toxicity of, 103
with bevacizumab, 99, 100
with interferon therapy, 102–103
interferon therapy compared to, 66, 102–103
mechanism of action, 23f, 24, 102
response to, 13, 61, 102–103
Thalidomide, 103–104
  in adjuvant therapy, 127, 130
  adverse effects and toxicity of, 104
  mechanism of action, 103
Thrombocytosis as prognostic factor, 41t, 45, 120
TNM staging of RCC, 4–6, 5t
  and prognosis, 35–39, 120
  and risk-based follow-up strategies, 11, 12t–13t
  in UCLA Integrated Staging System, 52, 53f
TroVax®, 65t, 67, 68t
Tuberous sclerosis complex 1 and 2 (TSC1/TSC2), 100
Tufts University analysis of surgery in metastatic RCC, 11
Tumor cell–based vaccines, 67
  in adjuvant therapy, 126t, 127
Tyrosine kinase inhibitors, 73–91
  in neoadjuvant therapy, 132
U
Ultrasonography in RCC, 3, 4
Unclassified type of RCC, 29, 32, 115
University of California Integrated Staging System, 6, 11, 52, 53f, 122–124, 123t
V
Vaccines, 61, 66–69
  dendritic cell, 66, 68t
  heat-shock protein-peptide complex, 67, 69, 126t, 130
  ongoing trials on, 68t
  tumor cell–based, 67
  in adjuvant therapy, 126t, 127
  viral vector–based, 67
Vascular endothelial growth factor, 46
  in clear cell RCC, 22, 23f, 24, 47
  in papillary RCC, 47
  as prognostic factor, 47, 55, 121
  as therapy target, 66, 95–100, 97f
VHL gene affecting expression of, 96
Vascular endothelial growth factor receptors, 96, 97f
Vena cava involvement
  as prognostic factor, 37t, 38–39
  staging of, 5t, 36t, 120
Venous involvement
  as prognostic factor, 37t, 38–39, 54t, 118t
  staging of, 5t, 36t, 120
Venous tumor thrombus, 6
  as prognostic factor, 37t
VHL gene, 46, 55
  and carbonic anhydrase IX expression, 47, 120
  in clear cell RCC, 21–22, 23f
  and vascular endothelial growth factor overexpression, 96
VHL protein
  in clear cell RCC, 22
  interaction with hypoxia-inducible factor, 22, 46, 48
  as prognostic factor, 46
Vimentin staining as prognostic indicator in RCC, 121
Viral vector–based vaccines, 67
Vitespen® (HSPPC-96), 126t, 130
Volociximab, 108–109
von Hippel-Lindau disease, 20, 22
von Hippel-Lindau gene. See VHL gene
W
Watchful waiting or active surveillance in RCC, 10
World Health Organization classification of renal cell neoplasms, 19, 20t, 32
WX-G250 immunotherapy, 69, 130