Renal Cell Carcinoma
Renal cell carcinoma represents a heterogeneous group of tumors, the most common of which is clear cell adenocarcinoma. The annual incidence of this tumor appears to be rising and approximately 12,000 individuals die from this cancer annually in the United States.

One third of patients who present have metastatic disease at the time of diagnosis, and another 40% who undergo nephrectomy will ultimately develop this complication. Over the past 10 years, a significant amount of new information concerning the epidemiology, molecular and immunologic characteristics, and therapy for patients with these tumors has appeared.

The recognition that inherited forms of renal cancer exist, and that chromosomal abnormalities can be identified in these tumors, suggested a genetic basis for renal cell carcinoma. The familial cancer syndrome, Von Hippel Lindau disease, provided the setting in which the genetic abnormalities associated with the development of renal cancer were first described. Abnormalities of the VHL gene have also been detected in sporadic clear cell carcinoma, and it has now been recognized that approximately 80% of these tumors will demonstrate characteristic alterations. Currently the functions of the VHL protein are being investigated, and the biology of clear cell carcinoma of the kidney is under study. Additionally, papillary carcinomas of the kidney appear to express different molecular defects, and these are now being unraveled.

Interest in the immunologic characteristics of renal cancer was based on some of the early observations suggesting spontaneous regression of this tumor and responses to immunologic-based therapy. Recently, it has been recognized that tumor-associated antigens may be present in selected renal cell carcinomas and that recognition of these antigenic structures by the immune system may occur. Additionally, abnormal immune regulation or immune dysfunction has also been described, with the molecular basis of these findings now being studied. The interaction between these two areas may have relevance for the effects of immune-based therapy. The treatment of renal cell carcinoma has also evolved, with improvements in surgical therapy for locally advanced tumors, the introduction of partial nephrectomy, and the recent description of laproscopic techniques for tumor removal. The understanding of the role of these modalities and their use in this patient population is now emerging.
For the majority of patients who have metastatic or advanced renal cell carcinoma that is not surgically curable, therapy remains of limited value. Continued investigation of cytokine-based therapy, adoptive immune strategies, and such newer strategies as the inhibition of angiogenesis is being conducted. Management of these patients often involves surgical removal of metastases and/or residual disease following therapy. Finally, the role of symptom palliation for this patient group is an important issue for individuals with this illness.

Renal Cell Carcinoma: Molecular Biology, Immunology, and Clinical Management was designed to assist physicians and researchers who treat and/or investigate patients with kidney cancer. This volume should assist urologists, medical oncologists, and radiation oncologists in their diagnosis and treatment of renal cell carcinoma. The review is designed to assess the pertinent clinical, biologic, and pathologic characteristics of this illness. New developments in the areas of molecular genetics and immune dysfunction have also been included, focusing on therapy for patients with renal malignancies. The roles of partial nephrectomy, radical nephrectomy, and laparoscopy are covered. Treatment of patients with metastatic disease remains a problematic area, and the modalities that have been used or are being developed are discussed.

The last decade has been a time of innovation in the management of renal cell carcinoma, and we believe that Renal Cell Carcinoma: Molecular Biology, Immunology, and Clinical Management will provide an overview of the field, as well as demonstrate the progress that has occurred in this area.

Ronald M. Bukowski
Andrew C. Novick
Renal cancer comprises 3% of all malignant tumors, with an estimated incidence of 39,000 new cases with 13,000 deaths in 2006 [1]. A study comparing 43,685 cases of renal cancer from 1973–1985 with those diagnosed in 1986–1998 (SEER database) demonstrated a marginal increase in the proportion of localized cancers and a decrease in advanced cases in the latter group. During the next 10-year period, however, the increase in localized and smaller tumors appears real, but overall survival (OS) differences are not yet apparent [2]. While increased imaging and laboratory testing may generally explain the increased incidence, other environmental factors may also play a role [2].

Historically, patients presented with the classic triad of symptoms including flank pain, hematuria, and a palpable abdominal mass; but recently, increasing numbers of individuals are being diagnosed when asymptomatic with an incidentally discovered renal mass. Advances in imaging and techniques have increased the percent of patients who are eligible for surgical intervention, but a significant percent of patients still present with surgically unresectable disease [3] or will subsequently develop metastatic disease.

Histology

The importance of histology in predicting the biologic characteristics and clinical behavior of renal cancers was recognized in the last decade. Renal cell carcinoma (RCC) represents a group of histologic subtypes with unique morphologic and genetic characteristics [4].

Clear-cell renal carcinoma is the most common type of renal cancer, accounting for ~70–85% of renal epithelial malignancies, and arises from the proximal convoluted tubule. Papillary renal cancer is the second most common type comprising 10–15% of renal tumors. Understanding histologic subtypes and associated gene alterations has provided the opportunity to develop targeted therapy, and has ultimately lead to the development of a new treatment paradigm.
von Hippel–Lindau (VHL) Syndrome

The von Hippel–Lindau (VHL) syndrome provided a unique opportunity to study the development of clear-cell tumors and delineate the genetic characteristics of this tumor. In sporadic renal cancer, both the maternal and paternal VHL alleles are inactivated by acquired mutations, whereas in the VHL syndrome the first mutation is inherited. Loss of VHL function may occur in ~60–80% cases of sporadic clearcell renal carcinomas [5].

The VHL protein is the product of the VHL gene, functions as a tumor-suppressor gene, and is responsible for ubiquination of hypoxia-inducible factor-α (HIF-α) and its subsequent degradation by the proteosome [5]. Under hypoxic conditions or in the presence of abnormal VHL function, HIF-α accumulates and activates the transcription of a variety of hypoxia-inducible genes. These include vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGF-β), transforming growth factor-α (TGF-α), and erythrythropoietin (EPO). The VHL gene may control this process by suppressing angiogenesis, but loss of the VHL gene or its function allow increased secretion of factors such as VEGF and produces the vascular phenotype characteristic of clear-cell carcinoma. Blocking components of the VEGF pathway and/or the function of HIF-α is currently the major therapeutic strategy for treatment or this malignancy, replacing immunotherapy with cytokines.

Systemic Therapy: Metastatic Disease

Immunotherapy consisting of interleukin-2 (IL-2) and/or interferon alpha (IFNα) had been the standard approaches for treatment of metastatic RCC, in addition to clinical trials investigating new agents. Responses were best with high-dose intravenous IL-2 (21%) compared to low-dose intravenous IL-2 (11%) and subcutaneous IL-2 (10%), although no survival advantage was observed [6]. Similar response rates were reported comparing high-dose IL-2 (23.2%) versus subcutaneous IL-2 plus IFNα (9.9%) and again, no improvement in time to progression (TTP) or survival [7] were seen.

IFNα has been established as the standard comparative treatment arm for Phase III clinical trials of new agents for the treatment of metastatic renal cancer. Several randomized trials have demonstrated improvement in medial survival for treated patients [8], and in a retrospective review a median OS of 13.1 months and a median TTP of 4.7 months for IFNα patients were reported [9].

A major advance in the field during the past 10 years has been the recognition that a variety of clinical characteristics can be used to categorize patients into groups with differences in prognosis. For previously untreated patients a prognostic model was developed by investigators at Memorial Sloan Kettering Cancer Center [9] and then validated and expanded. Five clinical characteristics were identified [9] and later validated at the Cleveland Clinic [10]. These prognostic criteria have been
utilized in Phase III clinical trials of the targeted agents, such as sorafenib, sunitinib, temsirolimus (CCI-779), and bevacizumab.

The cloning of the VHL tumor-suppressor gene and the elucidation of its role in up-regulating growth factors associated with angiogenesis have provided insights into RCC biology, as well as defining a series of potential targets for novel therapeutic approaches. The highly vascularized nature of this neoplasm has ultimately been utilized to control its growth and survival. VEGF and its receptors (VEGFR) are overexpressed in RCC compared to normal renal tissue, and VEGFR-2 is believed to be the major receptor mediating the angiogenic effects of VEGF [11]. The binding of VEGF to the extracellular domain of the VEGFR induces tyrosine autophosphorylation and subsequent increases in tumor-associated angiogenesis, endothelial cell proliferation, migration, and enhanced survival. During the past 5 years a number of agents inhibiting the VEGF pathway have been investigated in advanced RCC patients, and a series of these have produced significant clinical benefit including increases in progression-free and OS.

This group of novel agents has formed the central part of the new treatment paradigm for this tumor. The purpose of the current textbook is to provide an overview of these developments, as well as provide insights into the other targeted approaches that may ultimately play a role in the treatment of patients with this tumor. Chapters include a discussion of the biologic rationale for each target, as well as potential clinical approaches to provide inhibition of the pathway. The clinical data supporting the current approaches utilizing agents, such as sunitinib, sorafenib, temsirolimus, and bevacizumab, are outlined. In addition, novel targets including tumor necrosis factor, EGFR, Smac/DIABLO, and EpH2A are discussed in detail. The approval of three new agents for treatment of advanced RCC in 2007, and the likelihood that two additional drugs will receive regulatory approval in 2008–2009, make RCC a disease where not only significant clinical progress has occurred, but also an area that will be exploited to increase our understanding of how angiogenesis inhibitors function biologically and clinically.

The treatment paradigm for patients with localized and advanced RCC has changed dramatically in the last 5–10 years. Surgical advances are now mirrored by the dramatic changes in therapy available for metastatic disease. The collection of chapters in this text provides an update for urologists, medical oncologists, and researchers interested in the biology and therapy of this tumor.

Ronald M. Bukowski
Robert J. Motzer
Robert A. Figlin
References

Contents

1 Targeted Therapy for Metastatic Renal Cell Carcinoma: Introduction................................................................. 1
   Ronald M. Bukowski, Robert A. Figlin, and Robert J. Motzer

2 Renal Cell Carcinoma: Pathologic and Molecular Assessment of Targets .......................................................... 15
   Ferran Algaba

3 Genomic Assessment of Renal Cancer ........................................................................................................... 39
   Stephen M. Keefe, W. Kimryn Rathmell, and Katherine L. Nathanson

4 VHL and HIF in Clear Cell Renal Cell Carcinoma: Molecular Abnormalities and Potential Clinical Applications ....... 57
   Lucy Gossage

5 PBRM1: A Critical Subunit of the SWI/SNF Chromatin Remodeling Complex .................................................. 111
   Chung-Han Lee, Can G. Pham, and James J. Hsieh

6 Sporadic RCC: Abnormalities in Histone-Modifying Genes........................................................................... 153
   Ruhee Dere and Thai H. Ho

7 Genetic Heterogeneity in Renal Cell Carcinoma: Clinical Implications? ........................................................... 167
   Susan A. J. Vaziri, Mahrukh K. Ganapathi, and Ram N. Ganapathi

8 First-Generation Tyrosine Kinase Inhibitors: Clinical Results ............ 177
   Han Hsi Wong and Tim Eisen

9 Second-Generation Tyrosine Kinase Inhibitors (Pazopanib) in Renal Cell Carcinoma: Current Status ..................... 207
   Linda Cerbone and Cora N. Sternberg
10 Third-Generation TKIs (Axitinib, Tivozanib) in RCC: Enhanced Efficacy and Diminished Toxicity? ................................. 217
Hui Zhu and Brian I. Rini

11 Anti-VEGF and VEGFR Monoclonal Antibodies in RCC .............. 237
Bernard Escudier and Laurence Albiges

12 PI3-kinase, Akt, and mTOR Inhibitors in RCC ............................ 253
Daniel C. Cho and James W. Mier

13 Carbonic Anhydrase IX and Monoclonal Antibody G250: Relevance as a Clinical and Biologic Target in Renal Cell Carcinoma ............................................................ 263
Egbert Oosterwijk, Otto C. Boerman, Jeannette C. Oosterwijk-Wakka, Wim J. Oyen, and Peter F.A. Mulders

14 EGFR and HER2: Relevance in Renal Cell Carcinoma .................. 285
Sarathi Kalra and Eric Jonasch

15 The Role of Hepatocyte Growth Factor Pathway Signaling in Renal Cell Carcinoma .......................................................... 303
Fabiola Cecchi, Young H. Lee, Benedetta Peruzzi, Jean-Baptiste Lattouf, and Donald P. Bottaro

16 Development of Resistance to Targeted Therapy: Preclinical Findings and Clinical Relevance ........................................... 319
James W. Mier, Rupal S. Bhatt, David J. Panka, and Michael B. Atkins

17 Development of Combination Therapy with Targeted Agents .......... 349
C. Lance Cowey and Thomas E. Hutson

18 Side Effects of Targeted Therapy .................................................... 377
Luis León, Luis Miguel Antón-Aparicio, Emilio Esteban-González, Martin Lázaro-Quintela, and Sergio Vázquez Éstevez

19 The Role of Targeted Therapy in Special Populations .................... 417
James M. G. Larkin and Martin E. Gore

20 Immunotherapy: The Current Role of Cytokines ......................... 441
Mayer Fishman

21 Immune Checkpoint Inhibitors (Anti-CTLA4, Anti-PD-1) in RCC ................................................................. 469
Alexandra S. Bailey and David F. McDermott

22 Vaccines in RCC: Clinical and Biological Relevance .................... 483
Devin B. Lowe, James H. Finke, Jorge A. Garcia, and Walter J. Storkus
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Development and Incorporation of Biomarkers in RCC Therapeutics</td>
<td>527</td>
</tr>
<tr>
<td></td>
<td>Sumanta K. Pal and Robert A. Figlin</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Molecularly Targeted Staging Strategies in Renal Cell Carcinoma</td>
<td>541</td>
</tr>
<tr>
<td></td>
<td>Steven G. Koopman, Ali-Reza Sharif-Afshar, Robert A. Figlin, and Hyung L. Kim</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Clinical Prognostic Factors in Metastatic Renal Cell Carcinoma</td>
<td>555</td>
</tr>
<tr>
<td></td>
<td>Nimira Alimohamed, Toni K. Choueiri, and Daniel Y.C. Heng</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>The Role of Advocacy in Renal Cell Carcinoma</td>
<td>569</td>
</tr>
<tr>
<td></td>
<td>William P. Bro and Paul Larson</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Index</td>
<td>601</td>
</tr>
</tbody>
</table>
Contributors

Laurence Albiges, M.D.  Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France

Ferran Algaba, M.D.  Department of Pathology, Fundacio Puigvert, Universitat Autonoma de Barcelona, Barcelona, Spain

Nimira Alimohamed, M.D.  Department of Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada

Luis Miguel Antón-Aparicio, M.D.  Department of Oncology Service, Teresa Herrera, A Coruna, Spain

Michael B. Atkins, M.D.  Georgetown-Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Alexandra S. Bailey, M.D.  Dana Farber Community Cancer Care, Weymouth, MA, USA

Rupal S. Bhatt, M.D., Ph.D.  Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Otto C. Boerman, Ph.D.  Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

Donald P. Bottaro, Ph.D.  Urologic Oncology Branch, CCR, NCI, National Institutes of Health, Bethesda, MD, USA

William P. Bro, B.S.B.  Kidney Cancer Association, Evanston, IL, USA

Ronald M. Bukowski, M.D.  Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, USA

Fabiola Cecchi, Ph.D.  Urologic Oncology Branch, CCR, NCI, National Institutes of Health, Bethesda, MD, USA
Linda Cerbone, M.D. Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy

Daniel C. Cho, M.D. Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Toni K. Choueiri, M.D. Department of Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

C. Lance Cowey, M.D. US Oncology Research, Baylor-Sammons Cancer Center, Dallas, TX, USA

Ruhee Dere, Ph.D. Center for Translation Cancer Research, Institute for Biosciences & Technology, Texas A&M Health Science Center, Houston, TX, USA

Tim Eisen, Ph.D., F.R.C.P. Cambridge University Health Partners, Addenbrooke’s Hospital, Cambridge, UK

Bernard Escudier, M.D. Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France

Sergio Vázquez-Éstevez, M.D. Department of Oncology, Hospital Universitario Lucas Augusti, Lugo, Spain

Robert A. Figlin, M.D., F.A.C.P. Department of Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

James H. Finke, Ph.D. Departments of Immunology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Mayer Fishman, M.D., Ph.D. Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Mahrukh K. Ganapathi, Ph.D. Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Ram N. Ganapathi, Ph.D. Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Jorge A. Garcia, M.D. Department of Solid Tumor Oncology, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Emilio Esteban-González, M.D. Department of Oncology Service, Hospital Universitario Central de Asturias, Oviedo Principado de Asturias, Spain

Martin E.-Gore, Ph.D., F.R.C.P. Department of Medicine, The Royal Marsden Hospital, London, UK

Lucy Gossage, M.R.C.P., M.Sc. Li Ka Shing Centre, Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK

Daniel Y.C. Heng, M.D., Ph.D. Department of Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada
Thai H. Ho, M.D., Ph.D. Division of Hematology and Oncology, Mayo Clinic Arizona, Scottsdale, AZ, USA

James J. Hsieh, M.D., Ph.D. Human Oncology Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Thomas E. Hutson, D.O., Pharm.D., F.A.C.P. Department of Oncology, Baylor-Sammons Cancer Centre, Dallas, TX, USA

Eric Jonasch, M.D. Department of Genitourinary Medical Oncology, The University of Texas, Houston, TX, USA

Sarathi Kalra, M.D. Department of Genitourinary Medical Oncology, The University of Texas, Houston, TX, USA

Stephen M. Keefe, M.D. Division of Hematology and Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Hyung L. Kim, M.D. Department of Surgery/Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Steven G. Koopman, M.D. Department of Surgery/Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

James M.G. Larkin, Ph.D., F.R.C.P. Department of Medicine, The Royal Marsden Hospital, London, UK

Paul Larson, M.S. Communications, Evanston, IL, USA

Jean-Baptiste Lattouf, M.D. Urologic Oncology Branch, CCR, NCI, National Institutes of Health, Bethesda, MD, USA

Chung-Han Lee, M.D., Ph.D. Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Young H. Lee, Ph.D. Urologic Oncology Branch, CCR, NCI, National Institutes of Health, Bethesda, MD, USA

Luis León, M.D. Department of Oncology, Hospital Clinico Universitario Santiago de Compostela, Santiago de Compostela, Spain

Devin B. Lowe, Ph.D. Departments of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

David F. McDermott, M.D. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

James W. Mier, M.D. Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Robert J. Motzer, M.D. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Peter F. A. Mulders, M.D., Ph.D. Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

Katherine L. Nathanson, M.D. Department of Medicine, Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Egbert Oosterwijk, Ph.D. Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

Jeannette C. Oosterwijk-Wakka, B.Sc. Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

Wim J. Oyen, M.D., Ph.D. Department of Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

Sumanta K. Pal, M.D. Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

David J. Panka, Ph.D. Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Benedetta Peruzzi, Ph.D. Urologic Oncology Branch, CCR, NCI, National Institutes of Health, Bethesda, MD, USA

Can G. Pham, Ph.D. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Martin Lázaro-Quintela, Ph.D. Department of Medicine/Oncology, Complexo Hospitalario Universitario de Vigo, Vigo, Pontevedra, Spain

W. Kimryn Rathmell, M.D., Ph.D. Department of Medicine and Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Brian I. Rini, M.D., F.A.C.P. Department of Solid Oncology, Cleveland Clinic Taussig Cancer Institute, Glickman Urological Institute, Cleveland, OH, USA

Ali-Reza Sharif-Afshar, M.D. Department of Surgery/Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Cora N. Sternberg, M.D., F.A.C.P. Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy

Walter J. Storkus, Ph.D. Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Susan A.J. Vaziri, Ph.D. Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

Han Hsi Wong, M.B., Ch.B. Ph.D. Cambridge University Health Partners, Addenbrooke’s Hospital, Cambridge, UK

Hui Zhu, M.D., Ph.D. Department of Solid Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA