

1st Edition Preface

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 cytokinebased 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.

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2nd Edition Preface

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 ubiquitination of hypoxia-inducible factor- α (HIF- α) and its subsequent degradation by the proteasome [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 erythropoietin (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 of this malignancy, replacing immunotherapy with cytokines.

Systemic Therapy: Metastatic Disease

Immunotherapy consisting of interleukin-2 (IL-2) and/or interferon alpha (IFN α) 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 IFN α (9.9%) and again, no improvement in time to progression (TTP) or survival [7] were seen.

IFN α 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 median 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 IFN α 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.

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